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Science of Behavior Change Common Fund Program

Meeting Report

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ABBREVIATIONS AND ACRONYMS

Acronym Name	Acronym Definition
ACC	anterior cingulate cortex
ANS	autonomic nervous system
BOLD	blood oxygenation level dependent
CET	cognitive enhancement therapy
CNS	central nervous system
D2R	dopamine receptor D2
DA	dopamine
dACC	dorsal anterior cingulate cortex
DLPFC	dorsolateral prefrontal cortex
EEG	electroencephalogram
EEfRT	Effort Expenditure for Rewards Task
fMRI	functional magnetic resonance imaging
IBMT	Integrative Body-Mind Training
mGluR5	metabotropic glutamate receptor 5
mPFC	medial prefrontal cortex
mRNA	messenger ribonucleic acid
NAcc	nucleus accumbens
NIA	National Institute on Aging
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
OD	NIH Office of the Director
OppNet	NIH Basic Behavioral and Social Science Opportunity Network
PET	positron emission tomography
PFC	prefrontal cortex
PTSD	post-traumatic stress disorder
RCT	randomized controlled trial
RDoC	Research Domain Criteria
SOBC	NIH Common Fund Science of Behavior Change Program
vlPFC	ventrolateral prefrontal cortex
vmPFC	ventromedial prefrontal cortex
VTA	ventral tegmental area

EXECUTIVE SUMMARY

Background and Purpose of the Workshop

Nearly 40 percent of premature mortality in the developed world is caused by unhealthful behaviors.[1] Changing these behaviors can be very hard. Achieving *sustained* change constitutes an even greater challenge. There is a great need for research that can inform the understanding of the mechanisms underlying deleterious behaviors and interventions to circumvent them, thereby promoting healthful behavior, preventing disease, and improving quality of life.

The National Institutes of Health (NIH) Science of Behavior Change (SOBC) Common Fund Program supports activities aimed at understanding all behavior change—developing and sustaining normal, healthful behaviors, changing unhealthful behaviors and habits, and intervening with various treatment approaches to change disordered, dysregulated behaviors that are symptoms of psychiatric disease. SOBC's *Harnessing Neuroplasticity for Behavior Change* meeting brought together a diverse group of scientists to present and discuss research that can inform understanding of the mechanisms of behavior change and help optimize manipulations for inducing and/or maintaining change. (See appendix 1 for the meeting agenda.)

The workshop participants (appendix 2) were charged with the task of reviewing the state-of-the-science to determine the value added by the integration of neurobiological measures into research on behavior change interventions, the challenges and limitations associated with bio-behavioral research approaches, and the related scientific, interpretive, and pragmatic issues.

The meeting focused on an evaluation of known neurobiological substrates, processes, and mechanisms that hold potential for informing the science of behavior change. Neurobiological information can act as a marker that *correlates with* response to interventions. In experimental designs, *moderators* can account for differences in response to the experimental treatment. For example, males might respond to a manipulation or intervention, but females do not. In this case, sex acts as a moderating variable for treatment effects or outcome. Neurobiological variables can also serve as moderators that determine the degree to which an individual responds to an intervention.

Mediating variables are those through which the experimental manipulation or treatment may induce its effect on the outcome of interest. For example, successful therapeutic behavior change may be dependent upon changes in cognitive processes, such as appraisal. In this case, appraisal is a mediating variable (although direct manipulation is subsequently necessary to determine causation). Neurobiological mechanisms acting as mediators *are also* potentially responsible for intervention-induced behavioral change (e.g., changes in pattern of neural

[1] Schroeder, S.A. (2007). We can do better—improving the health of the American people. *New England Journal of Medicine 357*(12), 1221-1228 (September 20).

activation, connectivity, default state, conduction efficiency). These mediating variables constitute the most promising targets for interventions.

At this meeting, participants discussed the use, or potential use, of neurobiological variables as predictors, biomarkers, moderators, or mediators in behavior change research. They examined the state-of-the-science in this area, identified current barriers in the field, and discussed future research priorities.

Perspective Presentations

Five invited experts (Drs. Warren Bickel, Carlo DiClemente, David MacKinnon, Gregory A. Miller, and Tor Wager) shared their views on neurobiological and behavioral research and the use of neurobiology in understanding and intervening for behavior change. Their presentations emphasized the great potential of research combining neurobiological measures with behavioral analyses. However, the experts cautioned against overly simplistic views and encouraged care when inferring causality. Although neurobiological markers can add substantial value to the science of behavior change, researchers must be aware of the underlying assumptions and limitations of each method. The experts also identified a need for systematic studies to gain a better temporal resolution of intervention effects.

The invited perspective speakers underscored the complex nature of human behavior and the processes that lead from healthful behaviors to unhealthful excesses. Additional work is needed to not only refine the available biomarkers, but also develop a systematic approach to understanding the very complex interactions of biological, psychological, and societal factors that lead to behavior change.

Research Presentations

Scientists studying neurobiological mechanisms of behavior change (Drs. Rachel Alison Adcock, Elliot Berkman, Amit Etkin, Mark George, Todd Heatherton, Matcheri Keshavan, Diana Martinez, Russell Poldrack, Rajita Sinha, Yi-Yuan Tang, and David Zald) presented research talks on neurobiological variables serving as biomarkers, predictors, moderators, mediators, or targets for behavior change. These presentations covered a wide range of topics including mapping neural circuits, activation networks, and motivation. The speakers reviewed the value of neurobiological studies in diverse phenotypes and identified endophenotypes that may be targeted selectively in intervention studies.

The participating scientists were cautious with regard to the identification of biomarker signatures that may be clinically relevant in the foreseeable future but generally considered the dopamine (DA) system and its projections a good first candidate. Dysregulation of the DA system may have implications in a broad range of phenotypes that include motivation and addiction, and early studies are under way that aim at modulating this system in pre-clinical studies.

The scientists emphasized the important role of the individual and his or her environment for behavioral change and discussed possible mechanisms that can account for non-linear changes in behaviors. These changes can be obtained even with brief interventions and are likely caused by changes in the internal representation of the outside world.

A Framework for Future Research from Correlational Research to Direct Intervention

A five-level continuum of research study designs (Figure 1) served as an organizing construct to guide the proceedings during the workshop. The invited speakers were asked to address the breadth of these types of studies including research designed to reveal (a) biomarkers as predictors of change, (b) neurobiological phenotypes for optimal personalized treatments, (c) brain circuit activation/engagement as mediators for intervention effects, and (d) brain processes that can be targeted to replace established behaviors with sustainable, improved behaviors.

Figure 1: Proposed Continuum of Research on Neurobiological Variables in Behavior Change Research

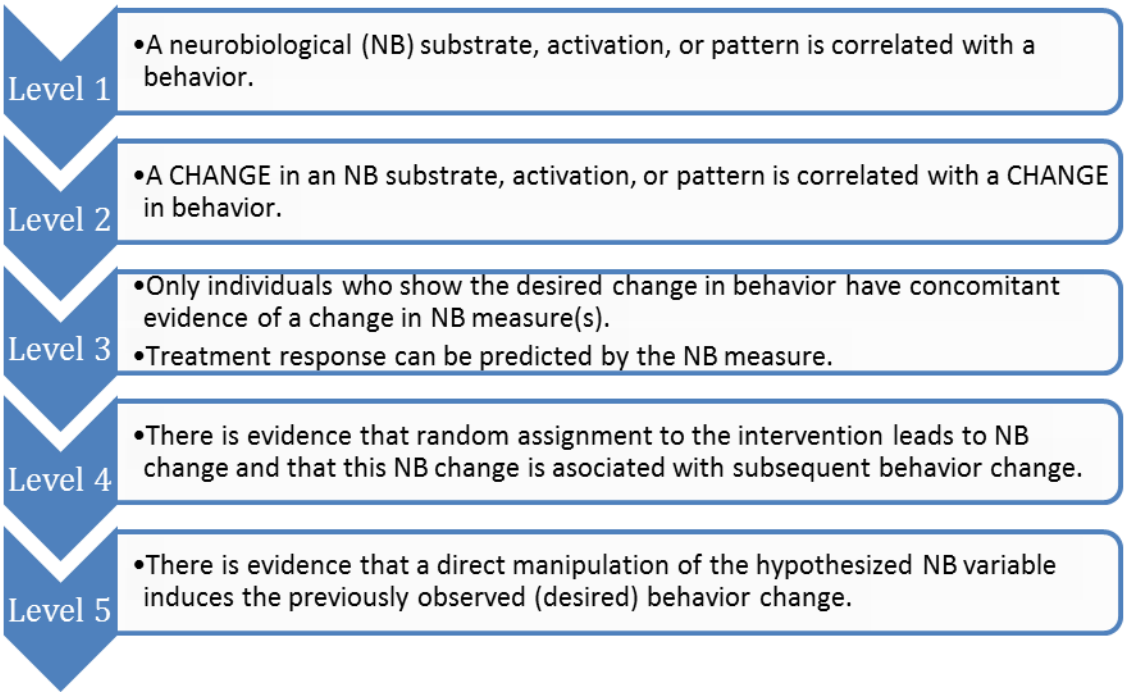


Table 1 displays an extended version of the continuum that incorporates feedback provided by the participants during the workshop. The five levels are meant to depict a logical flow of methodology from observational studies to randomized interventions that can lead to the identification of mediators. They do not intend to indicate a hierarchy of research priorities.

Table 1: Five Research Levels to Identify and Validate Markers, Moderators, and Mediators of Behavior Change

Level		Definition	Research Designs	Goals and Opportunities
1	a	A neurobiological substrate, activation, or pattern is associated with a behavior.	Cross sectional, single-measure research designs	Understand phenotype heterogeneity, identify markers, components, and endophenotypes
	b	A neurobiological substrate, activation, or pattern is linearly correlated with a behavior.	Quantitative research designs	Identify moderators that influence the magnitude of the correlation
2		A change in a neurobiological substrate, activation, or pattern is correlated with a change in behavior.	Longitudinal research designs with multiple measures	Understand individual differences in behavior change and identify neuronal substrates
3	a	Sensitivity established: The correlation between the neurobiological substrate and behavior is reliably detected.	Detailed tests of the activation pattern in different contexts	Make predictions about behavior change based on the biomarker
	b	Specificity established: The correlation between the neurobiological substrate and behavior is strong enough to make predictions.	Tests of similar contexts to establish boundary conditions	Distinguish markers that correlate with many traits from those that are specific
4	a	Random assignment to an intervention leads to a change in the neurobiological variable and in the behavior.	Multiple measures before and after the intervention	Understand whether the trait and the behavior are malleable and find individual differences
	b	Random assignment to an intervention leads to a change in the neurobiological variable and subsequent change in the behavior.	Dense measures before and after the intervention	Map the exact temporal order of changes in markers and behaviors
5		Direct manipulation of the hypothesized neurobiological variable induces the previously observed (desired) behavior change.	Experimental manipulation of the neurobiological variable	Validate the neurobiological variable as a mediator and declare it a target for future interventions

Participants indicated a need for refined methodology and additional resources in a number of areas of theoretical or practical research. Indeed, the participants identified opportunities for adding value from neurobiological studies at each of the five levels.

The **first level** comprises cross-sectional association or correlation studies that reveal relationships between behavior and a neurobiological substrate, activation, or pattern. Because these studies are based on snapshots at certain points in time, they yield no information about possible dynamic processes that underlie observed behavioral outcomes. They can still provide

a rich source for added value for behavioral studies. Neurobiological markers help to better understand outcomes, which may be comprised of multiple distinct components that are not apparent when studying the behavior alone. Similarly, these measures help researchers to better understand heterogeneity in treatment response.

The **second level** builds on the findings obtained in the first level by adding longitudinal observations to address the question of whether changes in the neurobiological variable over time correlate with changes in the behavior. Studies at this level do not yet contain targeted interventions. The presence or absence of correlations with biological substrates can help researchers further dissect behavioral change. Traditionally, there has been a tendency within behavior change programs to focus on predictors of stopping behaviors, which are very relevant for the field of drug addiction. Participants noted that finding predictors of positive behaviors, such as exercise or saving for retirement, are equally important. Future research may aim at identifying brain states that facilitate behavior change and measure an individual's capacity to resist unhealthful behaviors. Scientists' understanding of individuals' motivation to change is still very rudimentary. It is extremely difficult to define when a person "has changed." Long-term follow-up therefore appears to be an important ingredient of future studies on behavioral change.

The **third level** of study designs addresses the question of whether or not the neurobiological measure can be used to make meaningful predictions with regard to the behavior change. These studies thus aim to prove that the value added by the prediction outweighs the cost of obtaining the measure. In cases where this cannot be achieved, participants noted a need for more systematic efforts to look for other, more easily obtained measures (e.g., heart rate, hormone levels) as proxies. Sensitivity and specificity of these predictive tests have not been examined in sufficient detail in the past. During the workshop, examples were provided regarding the effort it takes to ensure that these tests are sufficiently sensitive and specific to be practically and clinically relevant. In the future, a more systematic approach to map predictors of behavioral change may lead to the identification of overlapping networks. Those predictors that correlate with positive changes across multiple domains would be the most valuable ones.

The **fourth level** introduces interventions into the study design. Level 4a includes research results that demonstrate that a randomized assignment to an intervention leads to a change in the neurobiological measure and in the behavior. Level 4b goes even further by establishing causality when the change in the neurobiological variable precedes the change in behavior. Participants noted that the malleability of the motor cortex shows individual differences and can be studied experimentally. It predicts learning capacity and decreases during depression. Whether or not this malleability correlates with other areas in the brain remains to be assessed systematically. Measurements of the neurobiological variables have to be conducted much more densely in the future to go beyond the pretest-posttest design and be sufficiently powered to establish a time course and causality and determine the ideal timing for the intervention. When interventions fail, several possible explanations may not have received enough attention in the past. Among these factors are the importance of the environment in

which the intervention is being conducted, competing interests, and general motivation, which are still very poorly understood. Even if an intervention is successful, there is still a substantial challenge ahead to maintain change for longer periods of time, and the predictors or biomarkers of adherence may be very different from the predictors of change.

The **fifth level** implies a direct manipulation of the neurobiological variable to induce the causally correlated behavior change. Participants noted that transcranial magnetic stimulation technology has reached a level where targeted, external stimulation of individual brain regions has become feasible. The identification of mediators that influence multiple networks of activity will provide the most efficient targets for direct manipulations, either by pharmacological or by other means.

In addition to the specific points above, participants identified several **general issues** and future challenges for the field:

- A systematic endeavor to identify the most promising neurobiological markers, moderators, and mediators across all levels is needed.
- The peer review process may contribute to an over-emphasis on discovery and an insufficient focus on a careful assessment of features of available markers, including their sensitivity and specificity as predictors.
- Scientists have often not been careful enough in the use of language, which has led to the conflation of markers, moderators, and mediators. As indicated in Table 1, only study designs on levels 4b and higher can make inferences about causality and distinguish mediators from markers.
- Human behavioral studies on those levels that cannot infer causality can be informed by animal model studies. Increased use of such models can help to identify the neurobiological measures that constitute the best candidates for mediators.
- Sustained behavioral change at all levels will only be achievable with intervention designs that take a holistic approach and include multiple levels of analysis and consideration of the environment in which the intervention occurs. The behavioral change research field is, therefore, exceptionally broad and requires collaboration across a very wide range of disciplines. The SOBC and Basic Behavioral and Social Science Opportunity Network (OppNet) programs at NIH are highly appreciated initiatives to bridge this gap.[2]

Conclusions and Next Steps

The participants recognized the SOBC program's efforts in bringing scientists from diverse disciplines together in this workshop. They unanimously expressed excitement about new research opportunities created by the recent junction of the fields of neuroplasticity and behavior. Each field clearly has the potential to add significant value to the other.

[2] Information about OppNet activities can be found at http://oppnet.nih.gov, and information about past SOBC activities can be found at http://commonfund.nih.gov/Behaviorchange/.

There was considerable skepticism that strategies to further modify external rewards to achieve behavior change will be successful. Instead, participants requested more sophisticated approaches to identify mediators of behavioral change and to explore the states during which individuals may be more susceptible to change. They cautioned against overly reductionist approaches and emphasized the need to take internal factors (e.g., neurobiological variables and trait differences) as well as external factors (e.g., patient-physician relationship, treatment context) into account when designing interventions.

MEETING REPORT

Background

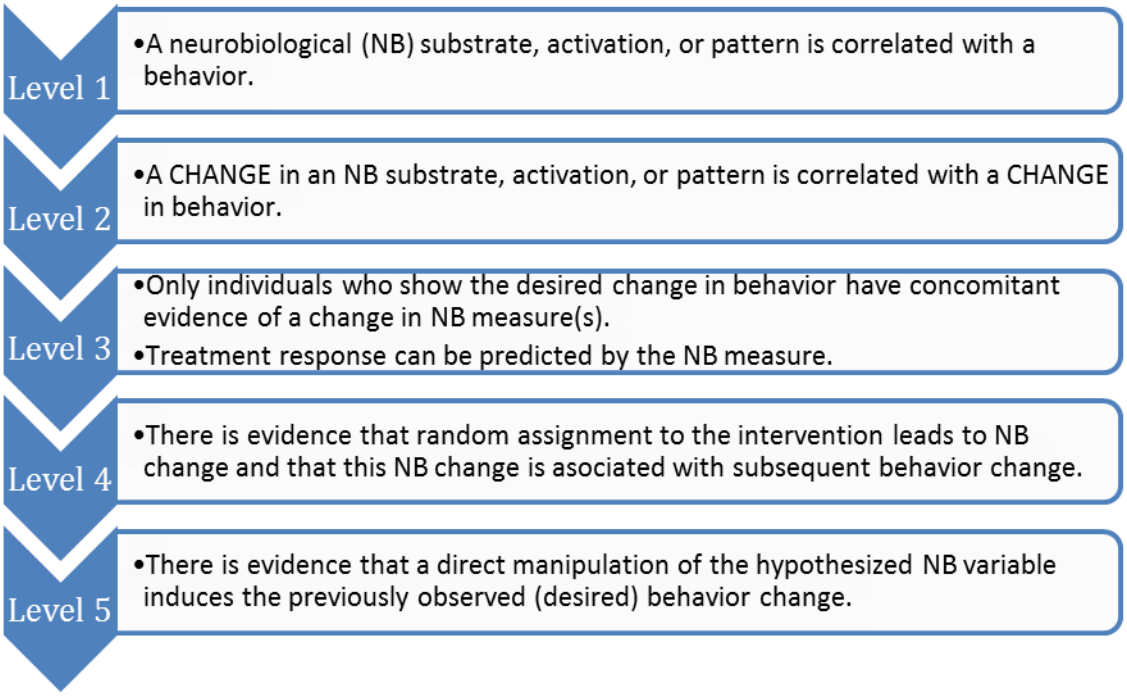
The Science of Behavior Change (SOBC) Program is supported by the National Institutes of Health (NIH) Common Fund and seeks to promote basic and translational research on the initiation, personalization, and maintenance of behavior change.[3] This meeting was planned to leverage NIH Blueprint investments in *Harnessing Neuroplasticity for Clinical Applications*[4] with a critical review and analysis by neurobiology and behavior intervention experts, representing basic and applied behavior change research across multiple disciplines. The meeting goal was to determine the potential contribution of neurobiological variables, measures, findings, and approaches to the understanding of processes and mechanisms of behavior change and to the refinement or development of more effective, long-term interventions.

Multiple NIH Institutes and Centers are interested in the principles, practices, and impediments of behavior change. The research and perspectives presented at this meeting are relevant to addressing behavioral causes of poor health, including overeating, unhealthful food choice, sedentary life style, smoking, and alcohol and substance abuse. Although a wealth of research exists about *how* to change a number of problem behaviors, many individuals are unsuccessful in their attempts to do so. In addition, relapse to former, well-practiced habits is common, and newly learned behaviors are not always sustained. The neurobiological mechanisms underlying behavior changes and the switch from short- to long-term change are relevant to the understanding of unhealthful behaviors as well as the behavioral manifestations of mental health disorders. Moreover, better use of neurobiological biomarkers has the potential to improve success rates by allowing for personalization and targeting of specific interventions. Ultimately, the ability to directly activate the circuits and mechanisms subserving sustained change, through behavioral, cognitive, or environmental interventions, is a research area that holds promise for intervening upon a variety of different behavioral problems.

To guide the proceedings during the workshop, the organizing committee drafted a five-level continuum of research study designs (Figure 1). The invited speakers were selected, in part, to address the breadth of these types of studies including research designed to reveal (a) biomarkers as predictors of change, (b) neurobiological phenotypes for optimal personalized treatments, (c) brain circuit activation/engagement as mediators for intervention effects, and (d) brain processes that can be targeted to replace established behaviors with sustainable, improved behaviors.

[3] See http://commonfund.nih.gov/behaviorchange/index.aspx.
[4] Cramer et al. (2011). Harnessing neuroplasticity for clinical applications. *Brain 134*, 1591-1609.

Figure 1: Proposed Continuum of Research on Neurobiological Variables in Behavior Change Research



Charge to the Participants

Minda Lynch, PhD, National Institute on Drug Abuse and Jonathan W. King, PhD, National Institute on Aging

Dr. Lynch thanked the more than 80 registered participants for their interest in this highly transdisciplinary workshop sponsored by the NIH SOBC Common Fund program[5] and invited participants to explore new avenues to extend and expand findings from brain plasticity to behavioral change and to apply neurobiological insights to reach sustained behavioral improvements. She encouraged the invited speakers to identify neurobiological measures as moderating and mediating factors and to hone in on mechanisms that can be used as targets for manipulations.

The agenda was created to stimulate discussions of the best use of technologies and methods and of biomarkers as predictors and markers for personalized medicine. Dr. Lynch reminded the audience that the SOBC initiative is concerned with behavioral change across a continuum of healthful and unhealthful behaviors and includes dysregulated behaviors during psychiatric conditions. She further noted a need to discuss neurobiological substrates in the clinical area and to characterize research that is ready to inform clinical approaches.

[5] The agenda and participant list can be found in the appendices.

Dr. King provided a brief background of the SOBC program, which started in 2010 and aims to bring together the communities involved in behavioral change efforts, often funded by a diverse set of Institutes and Centers across NIH. This fragmentation of efforts has meant that even people researching very closely related questions sometimes do not know of each other's efforts. The trans-NIH SOBC initiative provides an important vehicle for these scientists to exchange knowledge. The current workshop was the third trans-NIH conference sponsored by the SOBC since 2009.[6] Dr. King thanked the participants in advance for their contributions, which will inform future efforts of the SOBC program.

Welcome Remarks: NIH Common Fund SOBC Program

The co-chairs of the SOBC Working Group, Drs. Patricia Grady, National Institute of Nursing Research, Richard Hodes, National Institute on Aging (NIA), and Richard Suzman, NIA, provided welcoming remarks to the group. Dr. Grady noted that Common Fund support of the SOBC program speaks to NIH's commitment to SOBC's goals. The field of neuroscience has grown tremendously in recent years, as has the field of behavioral science. The SOBC program is aimed at bringing these two fields together. A meeting like this would have not been possible in the not very distant past, because scientists did not know very much about neuroplasticity, nor how to harness it for behavior change. Dr. Grady thanked the participants for helping the SOBC program staff identify exciting new research areas and determine future priorities.

Dr. Hodes emphasized the importance of the program by noting that he has been hearing repeatedly from scientists all across NIH that scientific knowledge regarding prevention and treatment of diseases frequently fails to translate into health improvements in applied or clinical settings. He also pointed to the tremendous advances that have been made in recent years in uniting neuroscience and the behavioral sciences. The current workshop provides an exciting opportunity to show that the boundary between the two has softened significantly.

Dr. Suzman reported that he attended a meeting convened by the National Academy of Sciences in the previous week on the role of behaviors for premature mortality and disability-adjusted life years. One calculation by Dr. Christopher Murray showed that about 50 percent of premature mortality and about one-third of disability-adjusted life years can be attributed to behaviors. That is an impressive amount. Dr. Suzman considered the SOBC program, where Institutes learn from each other, one of the best initiatives to address these issues.

[6] Meeting reports from SOBC trans-NIH workshops and Annual Meetings of Investigators can be found at https://commonfund.nih.gov/behaviorchange/meetings.aspx.

Perspective Presentation

What I Gained by Incorporating Neurobiological Concepts and Measures into Ongoing Research on Behavior Change: An Idiographic Account

Warren Bickel, PhD, Virginia Tech

Dr. Bickel described himself as a behavioral scientist by training with a long-standing interest in research on behavior change. In a brief review of his personal research journey, he identified several instances in which the addition of neurobiological markers has allowed him to explore new and exciting research avenues.

One of his main research interests is the study of temporal discounting—the observation that individuals prefer a smaller immediate reward to a longer-term larger benefit.[7] The exact ratio at which the tipping point is reached and the immediate reward becomes more attractive can be measured and shows substantial variability in a healthy control population. Temporal discounting can explain why many people have trouble incorporating health-promoting behaviors into their lives: the immediate reward (e.g., favorite sweet) is valued higher than the long-term benefit (e.g., maintaining a healthy weight).

Both too much and too little discounting are associated with mental diseases. Drug addicts, for example, have a very different temporal horizon compared to healthy controls: many do not think beyond the next 1-2 weeks. In the temporal discounting framework, the distant reward will, therefore, always be beyond their consideration. Anorexic patients, at the other end of the spectrum, tend to overcome the immediate pains of hunger for the greater good of a perceived ideal future body weight.

Until 2004, behavioral research on temporal discounting was focused on controlling impulses and modifying rewards to influence choices. A functional magnetic resonance imaging (fMRI) study[8] then showed that discounting is, indeed, a multi-component process: parts of the limbic system, including paralimbic cortex, are preferentially activated by decisions involving immediately available rewards, while regions of the lateral prefrontal cortex and posterior parietal cortex were engaged uniformly by choices occurring across time. Furthermore, the relative engagement of the two systems was shown to be directly associated with individuals' choices, with greater relative fronto-parietal activity when subjects choose longer-term options. Dr. Bickel realized that temporal discounting was driven by a two-part system: the limbic

[7] Madden, G.J., Petry, N.M., Badger, G.J., and Bickel, W.K. (1997). Impulsive and self-control choices in opioid-dependent patients and non-drug-using control participants: drug and monetary rewards. *Experimental and Clinical Psychopharmacology 5*, 256-262.

[8] McClure, S.M., Laibson, D.I., Loewenstein, G., and Cohen, J.D. (2004). Separate neural systems value immediate and delayed monetary rewards. *Science 306*, 503-507.

impulsive system and a cortical executive system.[9] In this model, disease is caused by an imbalance between the two competing systems.

Dr. Bickel then tested the hypothesis that working memory training, which strengthens the executive axis, can restore a temporal discounting balance that has been distorted toward the impulsive side. His research in 2011 showed that working memory training indeed reduced discounting of delayed rewards in stimulant addicts.[10] Furthermore, there was a positive correlation between discount rates and memory training performance.

In a recent meta-analysis of fMRI studies, Dr. Bickel and his colleague followed up on this finding and showed that a portion of the left lateral prefrontal cortex was a unique location in the brain where delay discounting and working memory processes overlap.[11] This area, they posited, represents a new therapeutic target for improving behaviors that rely on the integration of the recent past with the foreseeable future.

Preliminary results from additional recent studies further indicate that not only are the absolute values of temporal discounting interesting: the range of values found in cocaine addicts appears to be more restricted than in normal controls. The balance between the two systems thus may be more restricted for individuals in this disease state. Dr. Bickel is further investigating whether there may be a signature of change: preliminary data suggest that it may be possible to use baseline discounting data to predict which individuals will have the greatest likelihood to change their behaviors during an intervention.

In summary, Dr. Bickel drew valuable insights from neurobiological studies, which ultimately allowed him to make new predictions, study training of executive functions as a new treatment, explore possibilities to identify signatures that can predict behavior change, and to design new strategies for treatment personalization.

Panel 1 Research Talks

Races, Rewards, and Behavioral Change

David Zald, PhD, Vanderbilt University

Dr. Zald presented a conceptual approach to behavioral change that requires choices, such as the decision between eating unhealthful foods (i.e., immediate reward) or exercising (i.e., future benefit). The approach builds on perceptual decision-making models in which response options are characterized in terms of races in which neural information accrues over time for

[9] Bickel, W.K., Miller, M.L., Yi, R., Kowal, B.P., Lindquist, D.M., and Pitcock, J.A. (2007). Behavioral and neuroeconomics of drug addiction: competing neural systems and temporal discounting processes. *Drug and Alcohol Dependence 90*(Suppl 1), S85-91.

[10] Bickel, W.K., Yi, R., Landes, R.D., Hill, P.F., and Baxter, C. (2011). Remember the future: working memory training decreases delay discounting among stimulant addicts. *Biological Psychiatry 69*, 260-265.

[11] Wesley, M.J., and Bickel, W.K. (2013). Remember the Future II: Meta-analyses and functional overlap of working memory and delay discounting. *Biological Psychiatry*. Article in press DOI: 10.1016/j.biopsych.2013.08.008.

each option until one of the options passes a threshold and "wins" the race.[12] A similar race model can be applied to any condition in which a decision between response options exists.

Many different factors can bias the accrual of information and give one of the options a better chance of being selected to "win the neural race." Increased current reward value of one option, for example, will lead to faster accrual of evidence, because the reward is more highly valued. The temporal discounting paradigm can be easily conceptualized with this model. In rodents, for example, researchers have shown that orbitofrontal cortex neurons systematically prefer immediate rewards over delayed ones[13] and thus immediate options will accrue neural information faster than delayed options. The choice can also be biased by past reinforcement: if one option has a greater history of reward value (e.g., opioid exposure), then it will have stronger synapses on its side, will accumulate information faster, and reach the threshold faster.

The independent race model has been useful to model decisions and has been extended by a group of cortical models that allow for interactions. In these models, the inputs have the ability to inhibit each other. The interactive models thus not only allow for evidence to accumulate faster for one option, but also allow that option to decrease the rate of accrual of evidence for the other option.

Repetitive reinforcement can lead to automaticity: now one option not only accumulates evidence faster, but also starts at a different, elevated point, endowing this option with an advantage from the very beginning and may also slow down accrual of evidence for the other option. At the behavior level, repetitive reinforcement can lead to the development of habits. Scientists are now beginning to identify neurobiological substrates for these habits. They have observed that neuronal circuits involving the basal ganglia loops appear to be involved. Within these loops, a past history of long-term potentiation (LTP) leads populations of cells in the dorsolateral striatum to increase in signaling magnitude as a motor skill is learned.[14] These skills then become very easy to trigger and require little effort to execute because the efficiency of the circuit has changed. As a result, a reinforced option 1 may not only have faster accrual than a less reinforced option 2, but also require differential effort, which may impact utility judgments.

Dr. Zald noted that it might be feasible to feed fMRI activation results into the model under varying reward histories, option valuations, difficulty, and utility. These efforts may lead to identification of choice points that correlate with measurable activation signatures.

[12] Bogacz, R. (2007). Optimal decision-making theories: Linking neurobiology with behaviour. *Trends in Cognitive Sciences 11*, 118-125.
[13] Roesch, M.R., Taylor, A.R., and Schoenbaum, G. (2006). Encoding of time-discounted rewards in orbitofrontal cortex is independent of value representation. *Neuron 51*, 509-520.
[14] Beeler, J.A., Petzinger, G., and Jakowec, M.W. (2013). The enemy within: propagation of aberrant corticostriatal learning to cortical function in Parkinson's disease. *Frontiers in Neurology 4*, 134.

According to Zald's race model conceptualization, interventions can aim at directly increasing the chances for a less previously reinforced option 2 by putting breaks on the circuits that lead to faster accumulation of evidence for option 1. Alternatively, they can aim to make option 2 easier by modifying option 2 parameters (such as reward value or effort level) outside of a race context when only option is available. This will give option 2 a better chance of winning the race once both options are available.

He also reviewed work from his own lab developing the Effort Expenditure for Rewards Task (EEfRT) to measure the willingness of an individual to expend effort.[15] The EEfRT asks the subject if he or she will work harder for a larger reward. It can be done in an MRI scanner, where activation in ventral striatum correlates with choice.

Dr. Zald concluded by reviewing the role of DA in the behavioral choice paradigm.[16] Individual variations in DA signaling might be important for some of the biases and trait differences seen in human subjects. Imaging studies have, for example, shown that DA measures correlate with trait impulsivity, which will favor rapid decisions and make it harder for a long-term benefit (i.e., option 2) to win. But DA is not only a negative factor, but also a possible aide in the learning process itself due to its critical role in reinforcement-induced plasticity.

Increased DA signaling may also increase an individual's willingness to choose harder tasks. Previous work has shown that rodents will work harder for a greater reward, but when DA is depleted experimentally, they will no longer invest the extra effort.[17] Conversely, enhanced DA activation can prompt an individual to put in greater effort. In the EEfRT, for example, giving subjects amphetamine increases their willingness to do the more difficult task.[18] Variability in DA signaling might therefore critically impact a person's willingness to perform the harder task.[19]

In summary, Dr. Zald explained the race model and its importance for understanding neurobiological mechanisms that lead to choices, habits, and behavioral change. He showed that the integration of neurobiological measurements and behavioral studies has led to the identification of a first outline of circuits that influence those race outcomes and pointed to individual differences that may be critical to modify the outcome of these races.

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[15] Treadway, M.T., Buckholtz, J.W., Schwartzman, A.N., Lambert, W.E., and Zald, D.H. (2009). Worth the 'EEfRT'? The effort expenditure for rewards task as an objective measure of motivation and anhedonia. *PLoS One 4*(8), e6598.

[16] Treadway, M.T., Buckholtz, J.W., Cowan, R.L., Woodward, N.D., Li, R., Ansari, M.S., Baldwin, R.M., Schwartzman, A.N., Kessler, R.M., and Zald, D.H. (2012). Dopaminergic mechanisms of individual differences in human effort-based decision-making. *The Journal of Neuroscience 32*, 6170-6176.

[17] Salamone, J.D., Correa, M., Farrar, A., and Mingote, S.M. (2007). Effort-related functions of nucleus accumbens dopamine and associated forebrain circuits. *Psychopharmacology (Berl.) 191*, 461-482.

[18] Wardle, M.C., Treadway, M.T., Mayo, L.M., Zald, D.H., and de Wit, H. (2011). Amping up effort: Effects of d-amphetamine on human effort-based decision-making. *Journal of Neuroscience 31*, 16597-16602.

[19] Treadway, M.T., Buckholtz, J.W., Cowan, R.L., Woodward, N.D., Li, R., Ansari, M.S., Baldwin, R.M., Schwartzman, A.N., Kessler, R.M., and Zald, D.H. (2012). Dopaminergic mechanisms of individual differences in human effort-based decision-making. *Journal of Neuroscience 32*, 6170-6176.

How Motivation Shapes Memory: When Is a Carrot Not a Carrot?

R. Alison Adcock, MD, PhD, Duke University

Dr. Adcock focused her talk on the context in which decisions are made. To understand decisions, scientists need to better understand how events in the world are represented in the brain, which not only stores any memory but also constantly filters and revises incoming signals and determines which of them will generate lasting memories.

She agreed with Dr. Bickel's notion that behavioral research in the past has largely and possibly excessively focused on incrementally changing rewards to change behaviors. But changes in behavior are often not incremental; at some point, the confluence of memories changes an individual's model of the world. Once this point has been reached, behaviors can change quite radically. Subjects refer to these events as life-changing moments. The memories that trigger these changes have been shown to require the hippocampus and its overlying medial temporal lobe cortex in a system called the declarative memory system.

The function of this system is not only to remember what happened, but also includes an array of cognitive functions that allow for learning from the past and planning for the future.[20] This system is, therefore, a main substrate for learning-based interventions in mental health. To be able to modulate this system, researchers must first understand better how incoming information becomes processed and stored.

Human memories are never exact, because neuromodulatory signaling systems filter all input. The midbrain DA system is in a prime position to act as such a modulator and help determine which memories will last. The hippocampus receives direct projections from midbrain DA neurons. DA has been shown to have a central role: if DA is present prior to stimulation, then the threshold for long-term potentiation (the long-lasting enhancement of signal transmission between two neurons) is lower. This allows for the creation of lasting memories. Without DA, plastic changes due to stimulation are transient and are lost in the long term.

Dr. Adcock studied this modulation by DA neurons in humans in a monetary incentive encoding experiment.[21] She showed participants varying amounts of money (i.e., the cue), followed by a picture (i.e., the target). Participants were promised that they would receive the money when they recalled the pictures correctly the next day. The results showed that reward anticipation drove midbrain DA activation.[22] This activation likely increases DA release in the hippocampus, although this remains to be demonstrated experimentally. Dr. Adcock further showed that scene recognition memory was better for those pictures associated with high versus low reward cues. This shows that intending to memorize something and actually being motivated to

[20] Shohamy, D., and Adcock, R.A. (2010). Dopamine and adaptive memory. *Trends in Cognitive Science 14*, 464-472.
[21] Adcock, R.A., Thangavel, A., Whitfield-Gabrieli, S., Knutson, B., and Gabrieli, J.D.E. (2006). Reward-motivated learning: Mesolimbic activation precedes memory formation. *Neuron 50*, 507-517.
[22] Carter, R.M., Macinnes, J.J., Huettel, S.A., and Adcock, R.A. (2009). Activation in the VTA and nucleus accumbens increases in anticipation of both gains and losses. *Frontiers in Behavioral Neuroscience 3*, 21.

memorize something are different processes. Neurobiological studies using fMRI techniques now allow researchers to look inside a previously black box and study how connectivity between midbrain and the hippocampus predicts memory formation. Dr. Adcock suggested that the observed dopaminergic activation pattern might constitute a candidate signature of motivation to learn.

The identification of this pattern opens additional research questions about its exact nature and meaning. One may speculate that the pattern reflects curiosity in the brain. Also, the role of the reward in eliciting the pattern is still poorly understood. To address this issue, Dr. Adcock presented results from studies that did not offer rewards for correct memorization but rather punishments for errors.[23] In these experiments, she used the threat of a mild shock for forgetting studied images to determine if there is something special about reward, or if the same mechanisms are active in an experimental design that uses the threat of punishment to motivate learning. She found that threat of shock did enhance memory, but that it involved activation of the amygdala and not the dopaminergic neurons in the ventral tegmental area (VTA) of the midbrain.

For the picture recognition task, both the activation of the VTA and amygdala could enhance performance, because their connections to the hippocampus and para-hippocampal areas, respectively, can support memory storage and retrieval of pictures. But for other tasks they may not be interchangeable. Dr. Adcock demonstrated this in a virtual water maze experiment that crucially involves the hippocampus' ability to store detailed representations of relationships.[24] In the water maze experiment, reward led to increased recall, while punishment led to decreased performance in finding the platform.

In more recent work, Dr. Adcock studied incidental memory and found similar results compared to the intentional memory experiments: reward motivation enhanced sensitivity to expectancy violations in the hippocampus, while punishment motivation enhanced sensitivity to expectancy violations in the cortical medial temporal lobe.[25] As predicted based on this specific substrate within the memory system, reward motivation, but not punishment motivation, resulted in better memory for the event that violated an expectancy acquired from previous experience.

Dr. Adcock briefly reviewed results from a current study funded through the National Institute of Mental Health (NIMH) Biobehavioral Research Awards for Innovative New Scientists

[23] Murty, V.P., Labar, K.S., and Adcock, R.A. (2012). Threat of punishment motivates memory encoding via amygdala, not midbrain, interactions with the medial temporal lobe. *Journal of Neuroscience 32*, 8969-8976.
[24] Murty, V.P., LaBar, K.S., Hamilton, D.A., and Adcock, R.A. (2011). Is all motivation good for learning? Dissociable influences of approach and avoidance motivation in declarative memory. *Learning & Memory (Cold Spring Harbor, N.Y.) 18*, 712-717.
[25] Murty, V.P., and Adcock, R.A. (2013 Mar 2013). Enriched encoding: Reward motivation organizes cortical networks for hippocampal detection of unexpected events. *Cerebral Cortex (New York, N.Y. : 1991)*. Epub ahead of print.

(BRAINS) initiative that aims to take these described experimental paradigms closer to the clinic and develop new therapies. She noticed in her research on individual differences that even in the reward condition some people showed anxiety or arousal responses, as opposed to the more common feeling of reward that follows DA activation. As predicted, these individuals did not benefit from the reward incentive. This shows that it is not enough to provide a reward; how the brain responds to the reward determines the outcome.

Finally, Dr. Adcock presented very recent results on "Behavioral Neurostimulation Microinterventions," during which release of neuromodulators, such as dopamine, is elicited behaviorally. Subjects were asked to get motivated, without being provided any further instructions. All subjects were studied by fMRI, but only one group was provided actual feedback on DA midbrain activation. Showing the actual strength of this pattern to the subjects improved activation in those subjects that had low activation in the pre-test measurements. Dr. Adcock noted that these kinds of interventions are associated with very low risks and provide researchers with opportunities not only to better understand wanting, but also to actually induce it behaviorally and to capitalize on the downstream effects.

Perspective Presentation

The Utility of Brain Biomarkers for Predicting and Understanding Behavior: Concepts, Cautions, and New Directions

Tor D. Wager, PhD, University of Colorado, Boulder

Brain-based biomarkers for pain and distress have the potential to transform the study of affective processes in health and across disorders. Human neuroimaging plays a unique role in this process by creating a bridge between neurophysiological systems that can be studied mechanistically and mental phenomena. Although neuroimaging data are routinely interpreted as though they were biomarkers, Dr. Wager cautioned the audience that most of them should not be treated as such, because they are often poorly defined and their sensitivity and specificity to particular mental phenomena have not been characterized.

Biomarkers are useful whenever scientists want to obtain objective measures in addition to the subject's response. They are hypothesized to be directly related to brain mechanisms and can be linked to animal models, a research avenue that is not open when only obtaining a subject's response. The behaviors that researchers care about are complex, as are self-reports. Pain reports, for example, can be analyzed into components correlated with nociception, fear, incentives, anchoring, and self-consistency. When studying people who report severe pain by fMRI, researchers thus make two assumptions:

- Biomarkers of activity are simpler than behaviors. They engage in fewer interactions with contexts and are, therefore, simpler to study and measure. This implies a certain level of reductionism. Previous hopes that biomarkers for complex diseases such as schizophrenia would be identified have been shown to be unrealistic.
- Results from biomarker studies can be aligned with animal studies.

In summary, biomarkers allow scientists to measure components of mental phenomena (e.g., pain) that are

- less subject to cultural and decision bias
- closer to biological systems and disease mechanisms
- more likely to map onto specific mechanisms
- possible to map onto homologous animal systems to leverage mechanistic research

Dr. Wager reviewed criteria for a good biomarker. In research on pain processing, for example, one can obtain reliable patterns that increase with noxious stimuli. But similar changes are also seen in a large number of other traits with considerable variations in the reported effect size. Furthermore, the question of whether physical and social pain have a shared representation in the brain has not been addressed sufficiently.

Overall, the fundamental problem is that these approaches have not yet led to the identification of valid biomarkers. There is a lack of definition regarding the exact activation pattern; the field needs to determine more exactly which voxels have to light up to call an experiment a replication of an earlier finding. Furthermore, the field knows too little about sensitivity of these phenomena and their effect sizes. Specificity constitutes another problem: how specific is the pattern, and would it also occur in response to a completely different stimulus? Until these questions have been answered, scientists do not know the actual diagnostic value of the proposed markers. They further cannot imply that effects will be the same in each individual.

The field is further dealing with considerable problems of direct replication of findings, which have generated a large body of conflicting literature. Also, the interpretation of findings has not always been sufficiently rigorous. One group may, for example, establish a consistent signal in amygdala. Another study may show that the amygdala is associated with threat. Does that mean that the first group is measuring threat? Dr. Wager cautioned against such simplistic assumptions, because amygdala neurons are heterogeneous and code many different patterns that may correspond to different behaviors. As an example, simulating different neuronal populations within the amygdala can show that tasks that activate different populations can produce fMRI patterns in the amygdala that are almost completely uncorrelated.

Based on the issues identified above, Dr. Wager concluded that regions of interest, which have been widely used to describe activation patterns, are often not a useful level of analysis because they are too coarse. The amygdala or the dorsolateral prefrontal cortex (DLPFC) cannot be used to map signatures of complex human behaviors because they average huge numbers of neurons and circuits. Patterns within the regions may be more diagnostic.

Ideally, researchers would prefer to identify a pattern of activation in the brain that has high specificity for the underlying behavior, emotion, or sensation. They would like to measure

activity in the brain and be able to conclude that the subject is, for example, feeling pain.[26] In reality, however, the brain fMRI response to pain might also be seen in many other contexts. Dr. Wager's group recently conducted a meta-analysis of 3,500 neuroimaging studies and found that certain areas of the brain are activated across a large number of different stimuli.[27] Dr. Wager provided several suggestions to refine current efforts to identify biomarkers. His proposal for a new way of conducting these studies included the identification of precise patterns and characterization of sensitivity and specificity.

In an illustrative example from his own work, Dr. Wager described the identification of fMRI-based biomarkers for pain, which he called the neurologic pain signature.[28] Across studies, the neurologic pain signature had greater than 90 percent sensitivity and specificity for pain on a per-person basis compared with other salient somatic and emotional events. His method to identify such signatures can be applied to existing and new fMRI datasets, accelerating the fMRI biomarker development and testing cycle. The neurologic pain signature may be used to compare pain treatments at the neurophysiological level and provide a beginning point for deconstructing pain as a unitary experience. Finally, he presented data suggesting that it may be possible to develop fMRI-based signatures for multiple types of affect, providing new markers for study across disorders.

Group Discussion

Moderator: Lisbeth Nielsen, PhD, National Institute on Aging

The Value Added by Biomarker Studies

The speakers agreed that the spatial resolution of fMRI is still limited, but that it can nevertheless provide a very important linkage between external events and internal processes. More systematic efforts should be undertaken to find cost-effective peripheral markers, tests, and questionnaires that can be applied as proxies in large datasets to assess individual variation in behavioral domains of interest to SOBC.

There was also general agreement that more research is necessary to establish sensitivity and specificity of markers, but that the costs can be prohibitive. With limited resources at hand, prioritizing between an even better understanding of a specific marker of individual traits and the discovery of new correlations between activation patterns and particular behaviors can be difficult. A healthful balance between discovery and validation must be achieved.

[26] Wager, T.D., Rilling, J.K., Smith, E.E., Sokolik, A., Casey, K.L., Davidson, R.J., Kosslyn, S.M., Rose, R.M., and Cohen, J.D. (2004). Placebo-induced changes in fMRI in the anticipation and experience of pain. *Science 303*, 1162-1167.
[27] Yarkoni, T., Poldrack, R.A., Nichols, T.E., Van Essen, D.C., and Wager, T.D. (2011). Large-scale automated synthesis of human functional neuroimaging data. *Nature Methods 8*, 665-670.
[28] Wager, T.D., Atlas, L.Y., Lindquist, M.A., Roy, M., Woo, C.-W., and Kross, E. (2013). An fMRI-based neurologic signature of physical pain. *New England Journal of Medicine 368*, 1388-1397.

Small changes in experimental paradigms can change results substantially. Mapping these changes systematically will require substantial effort and expense. This means that scientists will likely have to focus on the most promising work for intense follow-up studies. Participants noted that in the context of studies of motivated behavior, dopamine imaging may be closest to becoming a valuable tool to aid diagnostics and may be a first candidate for such systematic efforts.

The predictive power of neurobiological markers has not been compared systematically to other measures, and it has not always been clear how much better the predictions based on newly identified biomarkers are compared to predictions based on the observed behaviors themselves.

Participants suggested deep brain stimulation as one method of intervening to change neuronal activation patterns directly and establish that this change leads to behavior change. This approach can confirm a causal relationship between the biomarker and the behavior and will have clinical relevance when it leads to measurable behavioral changes in individual study participants.

Biomarkers are important to identify and measure state and dispositional differences across individuals. The goal is to identify signatures that can predict which intervention is most likely to succeed in modifying behavior. Participants cautioned that most of the suggested signatures have not undergone the necessary scrutiny to establish their sensitivity and specificity.

Timing and the External Context of Interventions

Correct timing of measurements is crucially important when detecting trait differences, which otherwise may be masked by external pressures. A good understanding of the window of opportunity for behavioral change is lacking.

Participants agreed that interventions have the best chance of success when they occur in the environment in which the unwanted behavior is an option. It may, however, frequently be necessary to remove the participant from that environment temporarily to strengthen the pathways that lead to the healthful option. In the race model presented by Dr. Zald this means that the alternative option must first be promoted to have a better chance of winning. Then the subject can return to the environment in which there is an actual choice.

There is a lack of knowledge regarding the time frame necessary to train the subject to choose the healthful option before returning to the real-world environment. Furthermore, more thought should be given to methods that can continue to reinforce the choice of the healthful behavior in the natural environment.

Clinical experience suggests that some changes occur slowly over time and some are instantaneous. Neurobiological measures may add value by determining which behaviors have the potential for rapid change. Dr. Adcock's results suggest that interventions that aim at

changing the individual's internal representation of the outside world and his or her expectations may have the best chance to achieve non-linear change.

Extrinsic Versus Intrinsic Motivation

Most research provides extrinsic motivators (e.g., monetary rewards), yet the phenomenon of intrinsic motivation is still very poorly understood. It is not known if intrinsic motivation may lead to longer-lasting changes than extrinsic motivation.

Intrinsic motivation underlies substantial individual variation. Dr. Zald, for example, has observed occasional subjects in his experiment who would always try to get the reward that was more difficult to achieve irrespective of the external monetary reward. Their intrinsic motivation to meet a challenge was clearly more motivating than the extrinsic reward.

Neurobiological measures may at least help to understand whether or not the extrinsic motivators actually work and cause changes in the brain. The participants were generally skeptical toward the prospect that further tweaking of external rewards will lead to better success in behavior change.

Panel 2 Research Talks

Neurobiological Correlates of Craving and Addiction Relapse: Treatment Targets and Moderators

Rajita Sinha, PhD, Yale University

Dr. Sinha reviewed current knowledge regarding biomarkers and other predictors of relapse, which is very high for many addictions. A substantial number of known predictors of relapse exist:[29]

- Increased stress- and cue-induced drug craving predicts relapse.
- Childhood trauma is associated with lower limbic volume in substance dependence and influences relapse severity.
- Ventromedial prefrontal cortex (vmPFC) hyperexcitability in relaxed state and hypo-frontal response to stress predicts high craving and alcohol relapse risk.
- Smaller gray matter volume in medial frontal and posterior regions predict alcohol relapse.
- Sex-specific effects influence stress-induced amygdala reactivity and cocaine relapse.

Dr. Sinha emphasized that neuroplasticity and behavioral change are occurring in a dynamic context. Many different life events can lead to substantial changes in the states of the circuit of interest. Patients considered post-use and post-withdrawal are highly susceptible to cues. Dr. Sinha's research aims at understanding the factors that predict craving that leads back to drug use and the triggers of emotional states that lead to relapse.

[29] Sinha, R. (2011). New findings on biological factors predicting addiction relapse vulnerability. *Current Psychiatry Reports 13*, 398-405.

She reviewed results from an inpatient study involving subjects with 4 weeks of abstinence who participated in standard substance abuse treatment. In the laboratory environment they were then exposed to different kinds of cues followed by neuroimaging studies. These individuals were followed closely to get information about relapse after being discharged.

The study revealed a main effect of childhood trauma on brain volume in limbic areas, the hippocampus, and parahippocampal areas.[30] These effects were separable from the chronic effects of substance abuse, which are much more prominent in premotor areas. There was no detectable interaction between markers predicting relapse and those indicating chronic use. Childhood trauma showed a linear correlation with relapse; more severe trauma history predicted quicker relapse. Furthermore, the brain volume measured by voxel-based morphometry showed a linear negative correlation with the severity of relapse measured.

Dr. Sinha reviewed results from additional studies showing that drug craving can be measured reliably in the lab and that stress experienced in the lab predicted relapse. She provided an example where adding a biomarker to these predictions added value to predict relapse even more reliably. In this study,[31] she examined functional brain response to stress in alcoholics, who showed a disrupted neural response to stress and resting-state hyperactivity in the vmPFC and anterior cingulate cortex (ACC) brain areas. Under stress, alcoholics showed a blunted neural response in her experiments, which did not change considerably across different cue conditions. Dr. Sinha speculated that this might be a sign of neural inflexibility, where the system is trapped in one state and does not respond to changes in context. Analysis of the prospective follow-up data revealed that those patients who could activate their prefrontal cortex could, indeed, stay sober longer. The relative response or change over time that can be revealed by the fMRI thus correlates with the behavioral change.

Dr. Sinha emphasized the importance of the external context by reviewing data from a study on food intake in which she used normal, physiological stressors. Normal controls were subjected to euglycemia and hyperglycemia during an imaging session by using a hyperinsulinemic clamp. During each state, they were exposed to pictures of healthful and unhealthful food items. The goal of the study was to determine whether food preference shifts as a function of state (blood glucose) and type of food.[32] As glucose levels dropped down to 65, no clinical symptoms were visible, but plasma cortisol levels increased. This hypoglycemic stress increased preference and wanting of high-caloric foods and was correlated with limbic and striatal neural activations.

[30] Van Damm et al., *under review*.
[31] Seo, D., Lacadie, C.M., Tuit, K., Hong, K.-I., Constable, R.T., and Sinha, R. (2013). Disrupted ventromedial prefrontal function, alcohol craving, and subsequent relapse risk. *JAMA Psychiatry 70*, 727-739.
[32] Page, K.A., Seo, D., Aguier, R., Lacadie, C., Dzijuira, J., Naik, S., Amarnath, S., Constable, R.T., Sherwin, R.S., and Sinha, R. (2011). Circulating glucose modulates neural control of desire for high-calorie foods in humans. *The Journal of Clinical Investigation 121*, 4161-4169.

Dr. Sinha concluded that all predictors and moderators discussed in her talk were able to impact the neuroplasticity circuitry. She further emphasized the need to study neuroplasticity and change in the broader context and to consider motivational states. Clinical experience has demonstrated that relapse in the real world is subject to a humbling complexity that often leaves the patient and the treating physician puzzled about the reasons for the relapse. While acknowledging this complexity, researchers can still generate models that lead to good predictions at the group and at individual levels, identify targets for more effective treatments, and lead to a better understanding of how moderators such as sex and prior stress experiences affect specific neurobiological correlates.

Neurobiological Predictors in Interventions for Behavior Change

Diana Martinez, MD, Columbia University

Decades of animal research have shown that striatal dopamine signaling is crucial for reinforced behavior, and human positron emission tomography (PET) imaging studies almost unanimously suggest that addiction is associated with low dopamine receptor D2 (D2R) availability and low presynaptic DA release. In cocaine addiction, six previous imaging studies have shown low D2 binding and five have demonstrated low DA release compared to controls. These findings extend to other addictions (e.g., opiate, alcohol, methamphetamine, nicotine). Dr. Martinez considered the predictive value of PET imaging for clinical outcomes that may lead to targeted interventions. These interventions would aim at changing parameters that predict treatment response and that are malleable, which distinguishes them from other known predictive parameters such as time of previous drug use, which cannot be changed in retrospect.

She reported results from a laboratory PET imaging study that used raclopride as a radiotracer.[33] The first outcome measure was raclopride's binding potential, which provides information about DA binding and affinity. When subjects are given amphetamine to release presynaptic DA, the raclopride binding decreases because more receptors are occupied by DA. The second measure was DA release. Subjects in the study were provided a choice between cocaine and money. Those subjects who chose the cocaine had lower D2 binding levels.

In a second study, which was conducted during an actual treatment intervention, patients received monetary rewards (up to $1,000 for the entire study) for providing drug-free urine samples. A subgroup of the patients also took part in motivational therapy. The results showed that D2 receptor binding and DA release were higher in those subjects that responded to the treatment than in the non-responders. Surprisingly, binding and release in the responders were not different from values found in healthy controls. There was no difference in responders versus non-responders in age or the amount of cocaine use at study entry, but responders reported fewer years of use and had higher socio-economic status and employment rates. The

[33] Martinez, D., Carpenter, K.M., Liu, F., Slifstein, M., Broft, A., Friedman, A.C., Kumar, D., Van Heertum, R., Kleber, H.D., and Nunes, E. (2011). Imaging dopamine transmission in cocaine dependence: link between neurochemistry and response to treatment. *American Journal of Psychiatry 168*, 634-641.

results suggest that D2 receptor binding can indeed help to predict treatment response, and that this prediction may have clinical utility.

The next question is then whether scientists can increase D2 receptor binding to increase the chances for treatment success. In rodents, D2 overexpression has, indeed, been shown to reduce alcohol and cocaine intake. To aim to do this via gene therapy in humans may be a bold suggestion, but severe addiction has very high mortality, and studies on deep-brain stimulation have already been initiated. Preliminary results in non-human primates indicate that adeno-associated virus injections of a D2R overexpressing vector can increase D2 binding by up to 34 percent.[34]

Another way to increase DA signaling may be to find other neurotransmitter systems that modulate dopaminergic transmissions. Dr. Martinez reviewed the kappa opioid receptor system and the metabotropic glutamate receptor 5 (mGluR5) as potential candidate systems.[35] The idea that modulation of the kappa opioid receptor system may be clinically effective to treat addiction receives support from post-mortem studies in cocaine addiction that have shown that kappa receptors, pre-prodynorphin messenger ribonucleic acid (mRNA), and dynorphin are upregulated in cocaine abusers compared to control brains. Dr. Martinez will continue to pursue kappa opioid receptor imaging and mGluR5 as a possible target for DA modulation. More basic research is necessary to determine whether mGluR5 activation or antagonism will modulate the DA system in the desired direction.

Perspective Presentation

Designs and Methods for Studying Mediating and Moderating Neurobiological Variables in Behavior Change Outcome Studies

David P. MacKinnon, PhD, Arizona State University

Understanding the differences between moderators, mechanisms, and mediators is crucial to finding the best targets for successful interventions. The effects of interventions may differ across individuals. Dr. MacKinnon provided definitions of often used and confused terminology.

Mediator: A variable that is intermediate in the causal process relating an independent to a dependent variable.
Examples:

1) Motivational interviewing alters client language, which affects drinking outcomes
2) Exercise increases neurogenesis, which increases task performance
3) Therapy reduces craving, which reduces consumption

[34] Trifilieff, P., Feng, B., Urizar, E., Winiger, V., Ward, R.D., Taylor, K.M., Martinez, D., Moore, H., Balsam, P.D., Simpson, E.H., et al. (2013). Increasing dopamine D2 receptor expression in the adult nucleus accumbens enhances motivation. *Molecular Psychiatry 18*, 1025-1033.
[35] Trifilieff, P., and Martinez, D. (2013). Kappa-opioid receptor signaling in the striatum as a potential modulator of dopamine transmission in cocaine dependence. *Front Psychiatry 4*, 44.

4) Therapy increases self-regulation, which reduces alcohol consumption[36]

Mediation in behavior change research is important because (a) theoretical questions are about mediating processes; (b) identifying critical ingredients of successful interventions leads to more efficient treatments that are shorter and less expensive; (c) mediation provides a scientific approach to understanding how interventions have an effects; (d) mediation analysis extracts more information from a research study; and (e) mediation analysis presents many interesting statistical and mathematical issues.

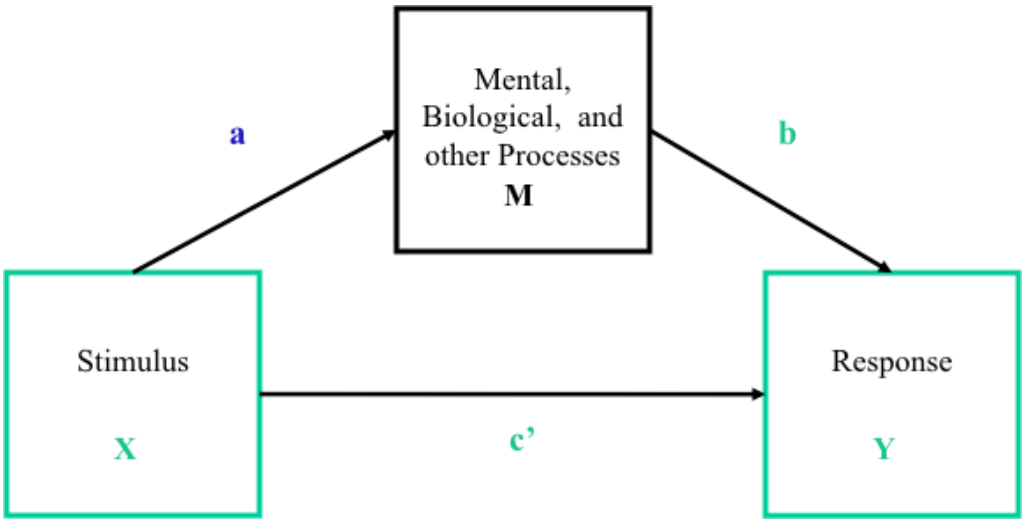
Moderator: A variable that affects the strength or direction of the relationship between X and Y. It is reasonable that the effects of interventions might differ across individuals.

Mechanism: A mechanism is the true underlying process by which one variable transmits its effect to another variable.[37] A way to measure the mechanism is needed.

The Stimulus-Organism-Response Mediator Model provides an illustration of mediation (see Figure 2). The stimulus and response are known, but what happens in between (mental and other processes) is less obvious. The mediation process is usually unobservable and may operate at different levels (e.g., individuals, neurons, cells, atoms, families, therapy groups, clinics, states). Multiple mediating processes may happen simultaneously and may be part of a longer chain. The researcher needs to define what part of a mediation chain to study. Mediation is about getting a better way to measure the mechanism(s). Regression equations can be used to test mediation.[38]

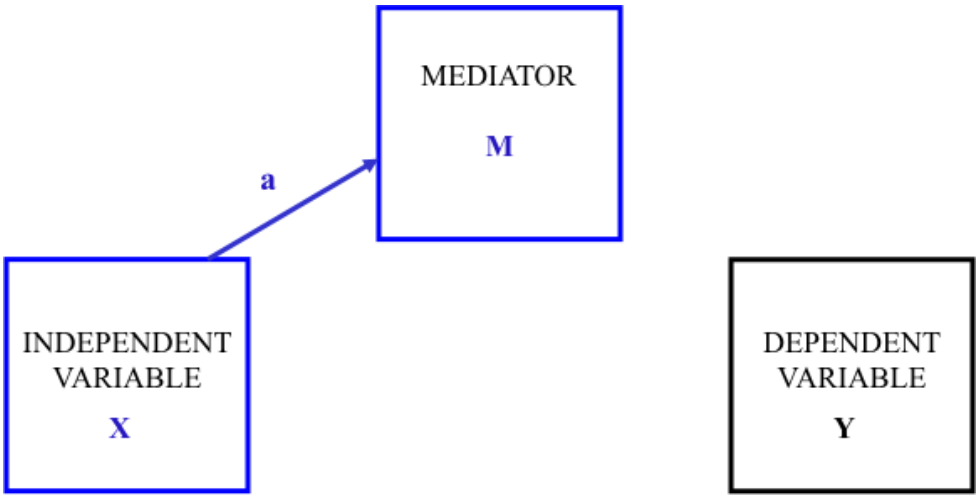
[36] Kelly, J.F., Stout, R.L., Magill, M., Tonigan, J.S., and Pagano, M.E. (2011). Spirituality in recovery: a lagged meditational analysis of Alcoholics Anonymous' principal theoretical mechanism of behavior change. *Alcoholism, Clinical and Experimental Research 35*, 454-463.
Moyers, T.B., Martin, T., Christopher, P.J., Houck, J.M., Tonigan, J.S., and Amrhein, P.C. Client language as a mediator of motivational interviewing efficacy: Where is the evidence? *Alcoholism, Clinical and Experimental Research 31*, 40-47.
Witkiewitz, K.A., Bowen, S., and Donovan, D.M. (2011). Moderating effects of a craving intervention on the relation between negative mood and heavy drinking following treatment for alcohol dependence. *Journal of Consulting and Clinical Psychology*, *79*, 54-63.
[37] See http://psychclassics.yorku.ca/MacMeehl/hypcon-intvar.htm.
[38] MacKinnon, D.P. (2008). *Introduction to Statistical Mediation Analysis*. New York: Erlbaum.
See also http://ripl.faculty.asu.edu/mediation/mediation-faq/ for more information about mediation analysis.

Figure 2. S-O-R Mediator Model



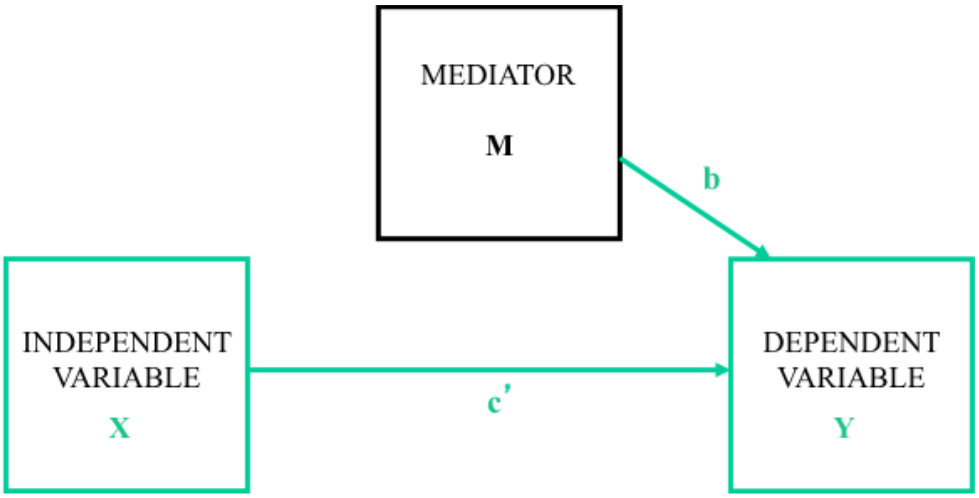
Dr. MacKinnon presented two mediation regression equations, which are depicted in Figures 3 and 4 below. The coefficients in the equations may be obtained using ordinary least squares regression, covariance structure analysis, or logistic regression. The product of coefficients test is the method of choice; it can also be applied to more complicated models such as the multiple mediator model. There are several inferential assumptions: (a) measures are reliable and valid; (b) data are a random sample from the population of interest; (c) the coefficients reflect true causal relationships and the correct functional form; (d) the mediation chain is correct; and (e) there are no moderator effects.

Figure 3. Regression Equation X on M



An independent variable is related to the potential mediator: $M = i_2 + \hat{a}X + e_2$

Figure 4. Regression Equation X and M on Y



The mediator is related to the dependent variable controlling for exposure to the independent variable: $Y = i_3 + c'X + bM + e_3$

Mediation analysis should be conducted even when there is no overall effect found for an intervention in order to determine if there is conceptual theory failure or if the mediator manipulation failed. There are two types of theories of the mediated effect: conceptual theory and action theory. Conceptual theory outlines how hypothesized mediators are linked to outcomes of interest; it addresses whether or not the right mediators are selected and whether or not they are causally related to the dependent variable. Action theory outlines how a manipulation relates to hypothesized mediators and addresses whether and how the selected mediators can be changed.

Both mediation and moderation effects are important to study because they allow the researcher to look at types of people and mediation at the same time. Mediation and moderation help investigators to understand how manipulations achieve effects and identify characteristics of participants and/or environments that moderate effectiveness of a manipulation. Treatments can be improved by understanding for whom and under what conditions they operate. Hypotheses can be tested regarding the specificity of results across groups. Finally, studying both mediation and moderation can inform differential treatment response and enable treatment development that better targets differential response in subgroups.

Causal inference for mediation is an active research area.[39] It is assumed that there are true causal relationships and that there is a self-contained, comprehensive model for regression analysis for mediation. The problem with mediation analysis is that the mediator is not

[39] See, for example, Pearl, J. (2009). *Causality* (2nd Ed.). New York: Cambridge.

randomly assigned, but self-selected. The assumption of "sequential ignorability" refers to the lack of confounders influencing mediation relations in the model.[40] Sensitivity analysis can be conducted to determine how large a confounder effect would be needed to eliminate the mediator effect. One way to deal with omitted variable bias and improve causal inference in a mediation study is to apply statistical approaches such as (a) instrumental variable methods; (b) principal stratification; (c) inverse probability weighting; and (d) G-estimation.[41]

There are also design approaches to improving causal inference. Statistical mediation analysis answers the question, "How does a researcher use measures of the hypothetical intervening process to increase the amount of information from a research study?" A follow-up question would be, "What is the best next study or studies to conduct after a statistical mediation analysis to test mediation theory?" The latter question can be answered with research designs that address consistency or specificity of the mediation relation.[42]

Dr. MacKinnon concluded his presentation by expressing hope that a better understanding of the methods provided herein will benefit the field's search for causal variables (i.e., mediators). He stated that mediation analysis is important because it provides information on how a treatment achieved its effects. Tests of mediation based on the product of the coefficients are the most accurate. Models with moderation and mediation are available. Longitudinal data analyses provide an ideal way to test for mediation. There are statistical methods and design approaches to address confounder bias and experimental designs to investigate mechanisms of the most effective treatments.

Group Discussion

Moderator: Susan Czajkowski, PhD, National Heart, Lung, and Blood Institute

Practical Considerations

The participant discussion focused on the practical applicability of neurobiological measurements and their relevance for real-world treatments. Imaging is very expensive and can be difficult to integrate into treatment regimes. But the societal consequences of addiction are also very costly. Therefore, whenever imaging adds sensitivity and specificity to existing measures, it may be of value to triage patients into the most promising intervention strategies. Even bolder thinking suggests that imaging might form the basis of gene-therapy or direct brain stimulation in the foreseeable future. The participants also identified a critical need to systematically identify cheaper proxy measures. Ultimately, the combination of peripheral and central neurobiological measures will likely constitute the most cost-effective option. Dr.

[40] Imai, K., Keele, L., and Tingley, D. (2010). A general approach to causal mediation analysis. *Psychological Methods, 15*, 309-334.

[41] G-estimation is a method of analysis based on structural nested failure time models (SNFTMs). See Robins, J. M., Blevins, D., Ritter, G., and Wulfsohn, M. (1992). G-estimation of the effect of prophylaxis therapy for pneumocystis carinii pneumonia on the survival of AIDS patients. *Epidemiology 3*, 319-336.

[42] MacKinnon, D.P., and Pirlott, A.G. (2012). *The unbearable lightness of b: Design approaches to causal interpretation of the M to Y relation.* Manuscript in preparation.

Martinez noted the critical importance of collaboration across different disciplines in these efforts: brain imaging experts may not be able to identify the most critical behavioral predictors to include, and vice versa.

Dopamine as Candidate Mediator

The DA system is a strong candidate as a true mediator for several behavioral outcomes, and more research is necessary to subject the measures obtained from this system to formal mediation analysis. The current research culture, however, is often strongly focused on discovery, which can make it difficult to obtain funding to exactly quantify mediation effects for which there is existing evidence. Large, clinical-trial type efforts will be required in the future to maximize power and include a sufficient number of possible confounders. For many efforts, it is not clear if the most promising approach would be to change the DA system directly, or to change individual traits that lead to different DA signaling patterns. With regard to the question of whether D2R signaling is a true mediator, changing it directly in the human brain by means of gene therapy would show whether or not it, indeed, changes an individual's chance to respond to treatment.

Participants pointed out the importance of brain measures and DA imaging to help scientists understand a model system and conceptualize drug use. The measure itself does not have to be scaled up to clinical use to be of great importance for downstream work. The field has made a lot of progress in recent years, and identifying the DA system as an important player has already added a lot of value to intervention strategies for treating addiction.

Participants further noted the importance of timing in real-world studies because it is easy to miss mediating effects if the measurement is carried out at the wrong time. Some measures are stable over time, making the timing less crucial, but many laboratory studies are based on single measures, and it is unclear how susceptible the results would be to changes in timing when embedded into larger longitudinal studies.

Panel 3 Research Talks

Training-Induced Changes in Inhibitory Control Network Activity

Elliot Berkman, PhD, University of Oregon

Self-control involves the ability to prevent or override unwanted thoughts, behaviors, and emotions and is integral to successful navigation of daily life.[43] Dr. Berkman considered whether it might be possible to train self-control by achieving lasting changes in inhibitory control network signaling (one component of self-control). These changes would be a very promising step to overcome the dominant response (e.g., bad habits) and lead to behavior change trans-diagnostically (i.e., not specific to a single behavior such as smoking, eating, addiction, academic achievement). Based on animal and lesion studies, the functional system behind inhibitory control is fairly well characterized. Patterns of activity in these known brain regions

[43] Muraven, M., Baumeister, R.F., and Tice, D.M. (1999). Longitudinal improvement of self-regulation through practice: building self-control strength through repeated exercise. *Journal of Social Psychology 139*, 446-457.

may be biomarkers of inhibitory control or self-regulation. This corresponds to the first level of the framework that the organizers of this workshop used to categorize research approaches. Researchers aim to reach the fifth and final levels that would validate the inhibitory control network as a mediator that can be activated to reach positive outcomes across a range of different behaviors.

As one important next step, Dr. Berkman addressed the second level of the framework by asking: "Now that we know what regions are in the network, how can we strengthen the networks?" There are currently no good behavioral interventions that strengthen them directly and, at the same time, allow for the study of the underlying neurobiological mechanism. Dr. Berkman thus used neuroimaging to address the question of how to train inhibitory control and track the induced changes. A literature review showed that traditionally, inhibitory control has been clustered with measures of executive function, which have been shown to increase with training in multiple studies. Some researchers have attempted to influence inhibitory control directly, but only a few examples of published failed attempts are available.[44] These may have failed either because inhibitory control cannot be improved, or because the interventions used did not reach a sufficient dosage to be effective and long lasting. Alternatively, the current paradigms may not have detected the change because the change happened somewhere else or at a different time than expected.

In his research,[45] Dr. Berkman chose a task that is known to activate inhibitory control networks[46] and studied the changes induced by training. This can be called a brain-training intervention. His research design, which involved 10 training sessions on an adaptive stop-signal task versus control task with pre- and post-training fMRI for both groups, further addressed the question whether the training might differentially affect activity in the self-control networks before and after the intervention. The results showed that this was indeed the case: activation in the dorsal anterior cingulate gyrus and the DLPFC increased during the preparation phase, in response to the trained anticipatory cue, but decreased in the implementation phase when stopping was actually required. This opposite activation pattern is consistent with the Dual Mechanisms of Control model, which suggests that a shift from reactive to proactive control can improve self-control performance, and might show that the brain is efficient in learning to engage inhibitory control in response to trained cues.

[44] Cohen, J.R., and Poldrack, R.A. (2008). Automaticity in motor sequence learning does not impair response inhibition. *Psychological Bulletin & Review 15*, 108-115.
Thorell, L.B., Lindqvist, S., Bergman Nutley, S., Bohlin, G., and Klingberg, T. (2009). Training and transfer effects of executive functions in preschool children. *Developmental Science 12*, 106-113.
[45] Berkman, E.T., Kahn, L.E., and Merchant, J.S. (in press). Training-induced changes in inhibitory control network activity. *Journal of Neuroscience*.
[46] Cohen, J.R., Berkman, E.T., and Lieberman, M.D. (2013). Intentional and incidental self-control in ventrolateral PFC. In D.T. Stuss and R.T. Knight (Eds.), *Principles of Frontal Lobe Function* (2nd ed) (pp. 417-440), New York: Oxford University Press.

These results may be directly relevant for future interventions designs and may explain why complex interventions that use a variety of non-predictable cues show the best transfer.[47] When the same cue is used, subjects will become accustomed to it, which is reflected by activation pattern changes in the brain. The brain is efficient at learning about the cue and responding specifically to that cue, which may work against generalization of the network activation. Interventions that do not use consistent cues may, therefore, result in the best generalization.

Dr. Berkman further showed that there was a linear relationship between activation of the DLPFC during the preparation phase and the basal ganglia during the implementation phase. This study shows that measuring the former can be used to make predictions about the latter, which corresponds to the third level of the framework guiding the workshop.

In summary, Dr. Berkman's results lend further evidence to the view that inhibitory control can indeed be trained, that the underlying neuronal activation patterns can be measured, and that these patterns have predictive value for training success. Dr. Berkman concluded that his results may explain differences in the field regarding the transferability of such training and emphasized the importance of the nature of the cue and the timing and context in which it is delivered.

What Do Neurobiological Variables and Measures *Buy Us* or *Add* to Research to Understand Behavior Change with Cognitive Remediation?

Matcheri S. Keshavan, MD, Harvard University

Dr. Keshavan reviewed the value added by incorporating neurobiological variables in schizophrenia research and how these variables can be used to guide interventions. The key questions are as follows:

- What are the neurobiological correlates of deficits in cognition and social cognition in schizophrenia?
- Do neurobiological measures change in relation to remediation of these deficits?
- Does neurobiological change correlate with behavioral change?
- Can we predict response to cognitive remediation by baseline neurobiological measures?

One important feature of schizophrenia is cognitive impairments (e.g., in working memory or in selective attention). These deficits are pervasive and persistent, present early and progress early during the disease, and predict functional disability.

[47] Muraven, M. (2010). Building self-control strength: Practicing self-control leads to improved self-control performance. *Journal of Experimental Social Psychology 46*, 465-468.

Previous work has shown that cognitive remediation is effective in schizophrenia with moderate levels of efficacy.[48] Cognitive enhancement therapy (CET), for example, has been demonstrated to be effective in chronic as well as early course schizophrenia. Imaging studies have shown gray matter increase or, at least, a lack of decrease when subjects were exposed to CET. These changes were seen in several key brain regions.[49] Furthermore, there was a positive linear correlation between the volume of the increase and the improvement during treatment.

These results point to possible moderators and mediators of CET effects. Dr. Keshavan conducted a path analysis that showed that CET effects on functional outcomes were influenced by neurocognitive measures and social cognition.[50] There may be many other factors that are beyond the scope of these first efforts.

Dr. Keshavan also discussed the concept of brain reserve and its importance for schizophrenia interventions. Studies in other phenotypes predict that individuals with larger reserves are better protected from the deleterious effect of the pathogenic changes. In Alzheimer's disease, for example, those with larger brain volumes may live longer until the deleterious effects of plaque accumulations appear as dementia.

Whether or not there is a brain reserve in schizophrenia had previously been addressed in only a small number of studies. Dr. Keshavan's research showed that baseline brain structure indexed by gray matter volumes and surface area appeared to moderate better response to cognitive remediation in early course schizophrenia and that the brain's functional reserve may be a potential moderator of response to cognitive remediation, as indexed by blood oxygenation level dependent (BOLD) responses to a cognitive control task.[51]

Dr. Keshavan concluded that these findings of increased brain volumes and changes in volumes during treatment were very valuable indicators to predict responders and non-responders. But they were expensive to obtain, and their specificity is currently not good enough to make them practically relevant. Greater efforts should be undertaken to find more specific and cost-effective proxy measures. Simple measures such as peripheral metabolites (e.g., plasma homovanilic acid to measure DA turnover) may be tried in the future.

[48] Wykes, T., Huddy, V., Cellard, C., McGurk, S.R., and Czobor, P. (2011). A meta-analysis of cognitive remediation for schizophrenia: Methodology and effect sizes. *American Journal of Psychiatry 168*, 472-485.
[49] Eack, S.M., Hogarty, G.E., Cho, R.Y., Prasad, K.M.R., Greenwald, D.P., Hogarty, S.S., and Keshavan, M.S. (2010). Neuroprotective effects of cognitive enhancement therapy against gray matter loss in early schizophrenia: Results from a 2-year randomized controlled trial. *Archives of General Psychiatry 67*, 674-682.
[50] Eack, S.M., Pogue-Geile, M.F., Greenwald, D.P., Hogarty, S.S., and Keshavan, M.S. (2011). Mechanisms of functional improvement in a 2-year trial of cognitive enhancement therapy for early schizophrenia. *Psychological Medicine 41*, 1253-1261.
[51] Keshavan, M.S., Eack, S.M., Wojtalik, J.A., Prasad, K.M.R., Francis, A.N., Bhojraj, T.S., Greenwald, D.P., and Hogarty, S.S. (2011). A broad cortical reserve accelerates response to cognitive enhancement therapy in early course schizophrenia. *Schizophrenia Research 130*, 123-129.

Emotional and Cognitive Mechanisms in the Treatment of Mood and Anxiety Disorders

Amit Etkin, MD, PhD, Stanford University

Dr. Etkin reviewed emotional and cognitive mechanisms in the treatment of mood and anxiety disorders and recent research strategies to understand moderators and mediators. His first research example was based on efforts to treat post-traumatic stress disorder (PTSD). Existing treatments (e.g., psychotherapy) show partial successes. Up to 50 percent of subjects still meet diagnostic criteria after the full treatment course. There is a great need for additional research, because evidence for next-step treatment after initial treatment failure is lacking, the neurobiological mechanisms for current treatments are unclear, and there are no known predictors of response.

Drs. Etkin and Wager recently conducted a meta-analysis of imaging results aimed at finding neuronal correlates of emotional and cognitive deficits in PTSD.[52] They identified hyperactivity in the amygdala and insula and a hypoactive medial prefrontal cortex (mPFC) as possible neurobiological markers. Another study showed impaired executive function and abnormal default-mode network activation.[53]

Dr. Etkin presented results from an interim analysis obtained from an NIMH-funded BRAINS study on the neurobiological mechanisms of prolonged exposure treatment for PTSD. The preliminary results suggest that prolonged exposure treatment decreases negative emotional reactivity and improves cognition and psychomotor speed. Improvements in PTSD symptoms are, however, not always strongly correlated with improvements in quality-of-life measures.[54] Dr. Etkin used a brain imaging study that measured neuronal activity before, during, and after a prolonged exposure intervention to determine whether or not the improvements in PTSD symptoms might be driven by distinct neurobiological pathways. The results showed that symptoms and functional impairment indeed appeared to correlate with distinct activation patterns. Improvements in PTSD symptoms were predicted by increased emotional reactivity and increased emotional regulation by the vmPFC, while improvements in real-world functioning were predicted by increased default mode network activation. The longitudinal design of the imaging analyses allowed the researchers to determine when changes in neuronal activity started to happen: they could see changes already after the fifth treatment session.

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[52] Etkin, A., and Wager, T.D. (2007). Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *American Journal of Psychiatry 164*, 1476-1488.

[53] Chen, A.C., and Etkin, A. (2013). Hippocampal network connectivity and activation differentiates post-traumatic stress disorder from generalized anxiety disorder. *Neuropsychopharmacology 38*, 1889-1898.

[54] Schnurr, P.P., Friedman, M.J., Engel, C.C., Foa, E.B., Shea, M.T., Chow, B.K., Resick, P.A., Thurston, V., Orsillo, S.M., Haug, R., et al. (2007). Cognitive behavioral therapy for posttraumatic stress disorder in women: A randomized controlled trial. JAMA *297*, 820-830.

Schnurr, P.P., and Lunney, C.A. (2012). Work-related outcomes among female veterans and service members after treatment of posttraumatic stress disorder. *Psychiatric Services (Washington, D.C.) 63*, 1072-1079.

Dr. Etkin concluded that psychotherapy decreases negative emotional reactivity and improves executive functioning (core deficits in PTSD). Imaging studies have led to the identification of predictive neural markers that have further allowed researchers to dissociate changes in symptoms versus changes in functioning. Preliminary data further suggest that activation of distinct emotion circuits may predict change in symptoms, while activation of cognitive circuits might predict changes in functioning.

In his second example, Dr. Etkin reviewed efforts to train cognitive and emotional circuitry in anxiety and depression. The key question is whether it might be possible to target these systems more directly through training, which might be able to remodel the brain and rehabilitate dysfunctional circuitries.

In a recent meta-analysis, his team found that neural response studies using negative stimuli showed greater response in the amygdala, insula, and dorsal anterior cingulate cortex (dACC) and lower response in the dorsal striatum and DLPFC in individuals with major depressive disorder compared to healthy subjects.[55]

In recent research, Dr. Etkin provided Internet-based working memory training to medication-free anxious depressed patients. Controls played Internet games that were not aimed at training these functions. The goal was to improve executive function and decrease emotional reactivity in the patients. Preliminary results suggest that it is, indeed, possible to target emotional reactivity and executive functioning with adaptive games that can be delivered online. The training changes were accompanied by neuronal circuitry changes that involved the amygdala, insula, and dACC. Furthermore, there was a dose-response relationship between training and improvement in symptoms, as well as some of these neural changes.

Dr. Etkin concluded that these results challenge those who work in the field to achieve more nuanced views of outcomes, and that neurobiological markers can often guide researchers where to look for heterogeneity.

[55] Hamilton, J.P., Etkin, A., Furman, D.J., Lemus, M.G., Johnson, R.F., and Gotlib, I.H. (2012). Functional neuroimaging of major depressive disorder: A meta-analysis and new integration of base line activation and neural response data. *American Journal of Psychiatry 169*, 693-703.

Perspective Presentation

The Critical Role of Neurobiological Variables in Understanding and Changing Human Behavior

Gregory A. Miller, PhD, University of California, Los Angeles

Dr. Miller was invited by the workshop organizers to provide an updated view based on his 2010 paper titled "Mistreating psychology in the decades of the brain," a position paper on the utility of brain-based explanations of psychological phenomena.[56] He emphasized the importance of neurobiological studies of behavior, but noted that researchers have not always been careful enough not to infer causality where pure association has been demonstrated. Terminology is not always just a matter of style; it becomes important when the use of certain phrases (e.g., calling schizophrenia a "biological disorder") increases the chances of obtaining grant funding. Especially during the "decade of the brain" there was a tendency to over-emphasize the role of biology and to ignore the validity of psychological constructs.

When, for example, researchers called schizophrenia a neurological disorder, what exactly did they imply? Did they mean that the disease has been found to be located in neurons? Similar questions can be raised when researchers talk about the genetic basis of a disease. There has been too much confusion in the past regarding the exact meaning of such phrases.

Dr. Miller reviewed several examples of publications, including those by leading scientists in the field, that he believes over-reached conclusions, and he suggested a possible influence from declaring the "decade of the brain" and the completion of the human genome project. He acknowledged the advances that research has made by integrating behavioral sciences with neurobiology, but he cautioned against far-reaching conclusions about the biological basis of disease. He also reviewed some of his own biological research on neuronal circuits that are disrupted in depression and anxiety and emphasized the importance of not reducing psychological research to the biological realm and supporting research that connects biological constructs back to psychological findings.[57]

The pendulum appears to have swung back since Dr. Miller's paper was published in 2010, and NIH conceptualizations of the relationships between psychological and biological phenomena have improved, especially due to NIMH's Research Domain Criteria (RDoC) initiative.[58] RDoC has restored psychological phenomena to the center of psychopathology and articulates its critical connections to genetics and neuroscience without claiming to reduce psychology to chemistry.

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[56] Miller, G.A. (2010). Mistreating psychology in the decades of the brain. *Perspectives on Psychological Science: A Journal of the Association for Psychological Science 5*, 716-743.

[57] Banich, M.T., Mackiewicz, K.L., Depue, B.E., Whitmer, A.J., Miller, G.A., and Heller, W. (2009). Cognitive control mechanisms, emotion and memory: a neural perspective with implications for psychopathology. *Neuroscience and Biobehavioral Reviews 33*, 613-630.

Silton, R.L., Heller, W., Towers, D.N., Engels, A.S., Spielberg, J.M., Edgar, J.C., Sass, S.M., Stewart, J.L., Sutton, B.P., Banich, M.T., et al. (2010). The time course of activity in dorsolateral prefrontal cortex and anterior cingulate cortex during top-down attentional control. *NeuroImage 50*, 1292-1302.

[58] See http://www.nimh.nih.gov/research-priorities/rdoc/index.shtml for information about RDoC.

Excessive reductionism seems to be declining within NIH, and as such, NIH is providing valuable leadership to the field.

Dr. Miller concluded his talk by noting that endophenotypes are often misunderstood to only include biological constructs. He advised participants to never pit nature against nurture or assume that biology underlies psychology. Researchers should avoid trying to localize phenomena that do not have a location and should never underestimate the complexity of gene by environment interactions. They should expand and harvest the evidence that psychological interventions change biology (not just the converse) and should remember that mental illness is mental—psychological—so the study of genes, neurons, and hormones is critically important but should not be the ultimate goal.

Group Discussion

Moderator: Varda Shoham, PhD, National Institute of Mental Health

Causality and Reductionism

Participants generally agreed with Dr. Miller that scientists have to use reductionist tools at times but should resist the seduction to infer causality when markers are found. The goal of harnessing neuroplasticity is not to replace psychology, but to identify potential value added to psychological research. Functional imaging has given new insights about what is going on below the observable changes. It thus has been a great tool to provide a different kind of information, but some scientists have not been careful enough to acknowledge its limitations.

Dr. Wager suggested that it would not be wrong to adopt the term brain disorder as long as researchers acknowledge the tremendous complexity that this implies. He also emphasized the importance of biological studies because our psychological constructs are not adequate to describe this complexity. Schizophrenia is not a single construct, just like cancer refers to at least 200 distinct disease mechanisms. If scientists understood what schizophrenia really is, then better treatments could be designed. Therefore, biological studies that do not map brain findings back to the domain of the mind are necessary, and intervening to change biology without changing mental states might very well make sense in different contexts.

Dr. Etkin added that some patients find relief in the suggestion that they are suffering from a brain disorder because somatic disease appears to be easier to accept and understand than explanations of mental disorders. He further pointed to the historic need to apply some level of reductionism to even begin to take on the challenge of understanding what goes on in the human brain. Now that the field of neuroscience has grown so dramatically, it may not be necessary to apply the same level of reductionism anymore. He agreed with Dr. Wager that not all brain functions need to map to psychological constructs. Glial cell activation, for example, is a very basic process that may be relevant for a multitude of different interventions. There is no need to connect all neurobiological observations back to psychological meaning.

Identification and Measurement of Individual Differences

Participants noted that the identification of sub-groups of patients always leads to further questions about underlying heterogeneity. When drug addicts respond to treatment, the question is raised whether they were true addicts, and whether they may be more motivated to get better, or have completely different motives to engage in behavioral change. It is also of great importance to take the external context into account when thinking about individual differences: drug addicts who have lost their jobs and houses already likely have a much harder time returning to their lives than those who still have their jobs and homes to which they can return.

The RDoC initiative reflects the great complexity behind individual variation by combining behavioral and neurobiological data. Dopamine, as relevant as it may be, is only one among many transmitters that may ultimately become clinically relevant. An additional source of complexity is the statistical nature of Diagnostic and Statistical Manual diagnosis; two people can both be called depressed and only share one symptom.

Currently used models to describe psychobiological processes are very crude, and the answer to increased complexity has often been to look for even greater receptor specificity rather than studying different psychological phenomena. Not only the biological processes, but also the psychological ones must be measured with greater granularity. This likely requires the development of better psychometric tools.

Panel 4 Research Talks

Brief Intervention Improves Self-control and Neuroplasticity: Mechanism and Application

Yi-Yuan Tang, PhD, Texas Tech University

Dr. Tang briefly reviewed emerging evidence that interventions based on meditation have the potential to ameliorate negative outcomes from deficits in self-control.[59] The beneficial effects of meditation are receiving increasing support from empirical studies on improving attention and cognitive functioning, the role of self-control in emotion, stress response and immune function, and well-being. Meditation may induce neuroplasticity and have application in the treatment of mental disorders.

[59] Hölzel, B.K., Carmody, J., Vangel, M., Congleton, C., Yerramsetti, S.M., Gard, T., and Lazar, S.W. (2011). Mindfulness practice leads to increases in regional brain gray matter density. *Psychiatry Research: Neuroimaging 191*, 36–43.
Lutz, A., Brefczynski-Lewis, J., Johnstone, T., and Davidson, R.J. (2008). Regulation of the neural circuitry of emotion by compassion meditation: effects of meditative expertise. *PLoS ONE 3*, e1897.
Tang, Y.-Y., Posner, M.I., and Rothbart, M.K. (2013). Meditation improves self-regulation over the life span. Ann. N. Y. Acad. Sci. Tang, Y.-Y., and Posner, M.I. (2013). Special issue on mindfulness neuroscience. *Social Cognitive & Affective Neuroscience 8*, 1–3.

He showed results from a brief experimental intervention aimed at understanding the underlying mechanisms of interventions targeting self-control. Based on the results, he then created an intervention for a mental disorder in a highly collaborative endeavor.

The meditation training used in his study targeted two self-regulation systems: the central nervous system (CNS) and autonomic nervous system (ANS). In a series of randomized controlled trials (RCTs), he and his collaborators showed that short-term Integrative Body-Mind Training (IBMT) improved attention and self-control in emotion, stress response, and immune function through CNS-ANS interactions. Study subjects participated in about 5-10 hours of IBMT over a 2- to 4-week period. This training led to structural changes in the brain related to the ACC and prefrontal cortex (PFC) in a known self-control network and changes in sympathetic nervous system activity.

To further understand the underlying mechanism, Dr. Tang used diffusion tensor imaging to identify possible changes in white matter.[60] He found that as little as 11 hours of IBMT increased fiber integrity in the anterior corona radiata, an important white-matter tract connecting the ACC to other brain structures. IBMT could thus provide a means for improving self-regulation and possibly reduce or prevent various mental disorders that are associated with disturbed self-regulation. Additional studies into the mechanisms of white matter changes showed that 11 hours of IBMT led to improved efficiency of white matter that involved increased myelin as well as other axonal changes.[61]

Dr. Tang has also studied IBMT in smoking cessation interventions.[62] He described results from an RCT that recruited non-treatment-seeking smokers. Smokers usually want to quit because of negative effects of smoking, but cannot. IBMT may induce the changes necessary to help them do so.

Results after 2 weeks showed that the IBMT group members reduced their smoking amount. Future studies are necessary to determine whether this is a lasting effect. The fMRI results showed that before training, smokers showed reduced activity in the ACC/PFC. After training, the IBMT group showed greater activity in the ACC but the control group, which received relaxation training, did not.

Dr. Tang concluded that brief interventions such as IBMT can induce unexpected behavior change. The smoking cessation study showed that reductions did not vary with prior self-reported intention. IBMT may thus be a low-cost and promising intervention to reduce smoking. Full-scale RCTs are necessary to replicate this mechanism on a larger scale.

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[60] Tang, Y.-Y., Lu, Q., Geng, X., Stein, E.A., Yang, Y., and Posner, M.I. (2010). Short-term meditation induces white matter changes in the anterior cingulate. *Proceedings of the National Academy of Sciences U.S.A. 107*, 15649-15652.

[61] Tang, Y.-Y., Lu, Q., Fan, M., Yang, Y., and Posner, M.I. (2012). Mechanisms of white matter changes induced by meditation. *Proceedings of the National Academy of Sciences U.S.A. 109*, 10570-10574.

[62] Tang, Y.-Y., Tang, R., and Posner, M.I. (2013). Brief meditation training induces smoking reduction. *Proceedings of the National Academy of Sciences U.S.A. 110*, 13971-13975.

Persistent Behavior Change through Automatic Mechanisms

Russell Poldrack, PhD, University of Texas at Austin

Dr. Poldrack presented research funded by OppNet that focuses on non-intentional behavior changes. It is based on a well-established idea from learning theory that fundamental differences exist between first-learned and later-learned behaviors. First-learned behaviors are the default behaviors that generalize over contexts and time. These first-learned behaviors are not deleted as they are replaced, but instead are retained in a latent state. This understanding helps to explain why a person can change a behavior at home (e.g., snacking on carrots instead of potato chips) but when in other contexts, the first-learned behavior of snacking on potato chips re-emerges. Later-learned behaviors are more contextually sensitive. The maintenance of later-learned behaviors might therefore require suppression of the first-learned behaviors and show poor generalization beyond the learning environment.

The first experimental paradigm Dr. Poldrack employed was based on the unconscious or automatic association of inhibition with a stimulus. He studied subjects' preference for food while they were hungry and shown junk food items. They were asked how much they would pay for each item in an initial auction procedure. All later research described herein is based on these initial preferences, which were used as a proxy for first-learned behaviors. The training involved a single-item stop signal: a certain type of cookie was, for example, always associated with a stop signal. After the training, the researchers probed the individuals' choices. During the probe phase, individuals were asked to choose between two items. The researchers always paired items together that had initially been associated with similar values. They also conducted a second auction to measure if the values associated with the different food items had changed. The first set of experiments based on this paradigm showed absolutely no effect. The research subjects did not value the items that had been associated with stop signals any lower than the other items.

Dr. Poldrack then designed an experiment to boost desired choices with a GO signal instead of using a stop signal. The results showed that he could indeed boost desired choices. Subjects were more likely to pick GO items, but this effect was only consistent for high-value items. This means that researchers were not successful in making people choose things they did not like, but could influence their choices among things that they liked from the start.

He further explored the mechanism behind the changed choices in a study of eye movements of subjects while engaged in the task. He found that people looked more at the item they are going to choose, and that people looked more at GO than at NO-GO items, even when they ended up not choosing the item. This means that the association with the GO signal may shift the subjects' attention toward the item with which it is associated. This shift in attention may be the mechanism that drives changes in preferences.

To study the maintenance of response choice, Dr. Poldrack brought the same subjects back 2 months later. On average, the participants in the study who received the most training (16

trials) demonstrated a marginal but significant boost for high-value items. The fact that the individuals did not choose low-value items that were associated with the GO signal remains to be explained, but for now it shows that they are not just choosing what they think the researchers want them to choose. The findings are preliminary and need to be replicated in additional studies.

In brain imaging studies, Dr. Poldrack found that GO training altered fronto-parietal activations and connectivity with the vmPFC. These results suggest that known systems of implicit control mechanisms and value computations are modified by the training exercise. The target of the intervention at the neurobiological level is thus to engage these known mechanisms.

Future goals of the project involve efforts to improve maintenance of learned behaviors. Dr. Poldrack is conducting additional experiments with altered spacing and under contextual variability. He concluded that non-intentional behavioral change is possible via approach-based training, but that the effect currently is restricted to high-value items.

Real Time fMRI Feedback and Smoking Cessation

Mark S. George, PhD, and Kathleen T. Brady, MD, PhD, Medical University of South Carolina

Dr. George discussed results from his collaboration with Dr. Brady on real-time fMRI feedback. The method is based on fMRI analysis of an individual's brain activity in the scanner, displaying brain activity to the individual in real time (in the scanner) via a thermometer bar, and asking the individual to try to actively change his or her brain activity. Real-time fMRI feedback techniques were developed several years ago and have shown promising results in studies of pain and mood modulation. The National Institute on Drug Abuse therefore funded several sites to conduct systematic studies of real-time fMRI feedback in substance use disorders, and Drs. George and Brady are funded to investigate its possible use in smoking cessation.

The specific aims of the current grant are to compare the use of real-time fMRI biofeedback to a non-feedback control group in terms of ability to decrease craving in nicotine-dependent cigarette smokers. In addition, subjects were tested for smoking cue reactivity in a human laboratory setting after the scanning sessions to examine the durability of any alterations seen in the scanner. The research team initially conducted several pilot studies to determine which variables to feed back to the research subjects, which region to study, and whether an intermittent or a constant feedback would be more likely to succeed. They started with studies in the motor system by asking subjects to imagine movement. They found that intermittent feedback worked better than continuous feedback.[63] They also found that no feedback as the control condition was better than false feedback, which led to frustration. With regard to the

[63] Johnson, K.A., Hartwell, K., LeMatty, T., Borckardt, J., Morgan, P.S., Govindarajan, K., Brady, K., and George, M.S. (2012). Intermittent "real-time" fMRI feedback is superior to continuous presentation for a motor imagery task: A pilot study. *Journal of Neuroimaging 22*, 58-66.

instructions given to the research subjects, "reduce craving," which is associated with reduced BOLD activity, performed better than "resist craving" and was therefore chosen.[64]

Participants completed three visits each with three feedback sessions per visit. After each fMRI session, subjects went to a laboratory setting where they were exposed to smoking-related cues and physiologic and subjective response to the cues were assessed. For the clinical trial, 40 participants were randomized to a feedback group or no feedback group. Subjects were not coached on how to try to reduce craving. The fMRI BOLD signal in the ACC decreased significantly in the biofeedback scan group but not in the control group.

The psychophysiological data from pre- and post-intervention measurements showed a difference in heart rate: those smokers who received feedback had lower heart rates when exposed to smoking-related cues. When asked about their urge to smoke, subjects with real feedback showed decreased peak craving during cues.

Dr. George concluded that real-time feedback of ACC activity to non-treatment-seeking smokers with the instruction to reduce ACC activity resulted in decreased psychophysiological responses to cues, even outside of the scanner. These responses were associated with decreased regional activation and decreased self-rated craving.

Future studies will aim at testing this paradigm for use in treatment-seeking smokers for smoking cessation. Parallel efforts are under way to determine a method to translate the fMRI imaging findings into less expensive proxies (e.g., electroencephalogram [EEG], near-infrared spectroscopy).

Biomarkers for Self-Regulation Failure

Todd F. Heatherton, PhD, Dartmouth College

Dr. Heatherton has carried out extensive studies of self-regulation failure. In a recent article, he addressed the question of why people lose control and fail to regulate their moods, impulses, and behaviors.[65] His summary revealed many threats to self-regulation that included exposure to cues, lapse activated consumption, negative mood, resource depletion, alcohol consumption, and prefrontal brain damage. All of these influences overwhelm prefrontal control or impair prefrontal functioning. In either case, the disruption of prefrontal-subcortical circuits lead to self-regulatory failure.

Dr. Heatherton reviewed the results from a brain imaging study on self-regulation with regard to food and sexual behavior. He addressed the question of whether individual differences in cue reactivity may predict weight gain in college freshmen, who often put on weight in the first

[64] Li, X., Hartwell, K.J., Borckardt, J., Prisciandaro, J.J., Saladin, M.E., Morgan, P.S., Johnson, K.A., Lematty, T., Brady, K.T., and George, M.S. (2013). Volitional reduction of anterior cingulate cortex activity produces decreased cue craving in smoking cessation: A preliminary real-time fMRI study. *Addiction Biology 18*, 739-748.
[65] Heatherton, T.F., and Wagner, D.D. (2011). Cognitive neuroscience of self-regulation failure. *Trends in Cognitive Science 15*, 132-139.

6 months of school. Study participants who were not aware of the fact that they were exposed to cues were shown pictures of food, tobacco products, or people engaging in sexual activity. The students said that they liked the sexual pictures the least, but spent most time looking at them before giving their answer to the question whether or not the picture contains a female person. Participating students gained on average 7.2 pounds 6 months later. Imaging study results showed that nucleus accumbens (NAcc) activity during exposure to food images at the first visit predicted an increase in body mass index at the second visit. This effect was specific to food images and not seen when exposed to the other cues. NAcc activity also predicted sexual desire when the subjects were exposed to sexual imagery. Imaging results for those who were more sexually active showed greater cue reactivity.[66]

Dr. Heatherton also described the results of a cohort (*n*=31 females) exposed to a food cue during fMRI. Investigators texted images of appetizing food seven times a day for 1 week and analyzed food consumption. Results of the study confirmed that subcortical activity in the NAcc was predictive of overeating and that prefrontal activity in the inferior frontal gyrus was predictive of less overeating. These results confirm a model in which PFC control is necessary to restrain the activity of subcortical regions of the brain during threats to self-regulation.

It is important to note that the subjects studied herein were not self-regulating in the moment. Instead, self-regulation is something that people do over long periods of time. The difficulty in this research is, therefore, to understand if and how self-regulation reflects individual differences in capacity to control behavior over time. Some people appear to be better than others at doing so. Dr. Heatherton is addressing this question by studying resting state functional connectivity. This method is based on the fact that brain regions that are active together become functionally coupled and become activated at rest. Researchers can use functional imaging to study the integrity of these networks and can determine whether there is individual variation and whether individual variation predicts self-regulatory outcomes.

Dr. Heatherton presented a study that tested individual differences in self-regulation capacity. His team gave a milkshake to chronic dieting study participants and analyzed brain activation patterns using fMRI. Investigators then measured the study participants' consumption of ice cream. Individuals with strong ventrolateral prefrontal cortex (vlPFC)-action observation network connectivity and weak vlPFC-frontal control connectivity consumed more ice cream. These results suggest a mechanism to account for the individual differences in self-regulation capacity.[67] Distinct activation patterns may prove predictive for individuals with low self-regulation abilities. These individuals can then be targeted for specific interventions. In more recent work, Dr. Heatherton investigated whether resting state network activity could predict percent body fat, which preliminary data suggest indeed seems to be the case.

[66] Demos, K. E., Heatherton, T. F., and Kelley, W. M. (2012). Individual differences in nucleus accumbens activity to food and sexual images predict weight gain and sexual behavior. *Journal of Neuroscience 32*, 5549-5552.
[67] Demos, K. E., Kelley, W. M., and Heatherton, T. F. (2011). Dietary restraint violations influence reward responses in nucleus accumbens and amygdala. *Journal of Cognitive Neuroscience 23*, 1952-1963.

In 1996, Baumeister and Heatherton conceived the strength model of self-regulation, which predicts individual variation in the strength to self-regulate.[68] It further predicts that people can increase their self-regulatory capacity by building that strength. Like a muscle, this capacity can become exhausted. The model has been helpful in many different contexts. Dr. Heatherton has been able to deplete people by showing them neutral movies that show words the subjects are supposed to ignore. In this model, he found that depletion is an amplifier of subcortical activity. Depletion thus breaks down the functional coupling of the capacity networks. In a final study, Dr. Heatherton depleted 39 dieters, who otherwise do not show much cue reactivity. He found that depletion-associated changes correlated with desire.[69]

From the interventions standpoint, it will be interesting to determine whether self-regulatory capacity can be strengthened. Meditation may be one existing activation intervention that helps people build a general domain capacity for self-regulation.

Group Discussion

Moderator: Minda Lynch, PhD, National Institute on Drug Abuse

Definition of Measures and Potential Proxies

Body fat is an organ that releases signal molecules that may act as peripheral markers. Other peripheral measures (e.g., heart rate) can also be of interest as markers of self-regulatory capacity. Participants cautioned against lack of detail in describing the intervention and the derived measures. Some meditation training styles, for example, aim to clear the mind, while others focus the mind on something specific. Researchers must be clear about what they are doing, what is expected of the subjects, and what exactly they are measuring. It would be further helpful to engage in more targeted approaches that explicitly focus on the identification of mediators.

No single biomarker will be a panacea for behavioral change. It may be possible to combine the described approaches and, for example, use real-time fMRI feedback to train meditation and enhance its effects. Other peripheral measures such as the EEG may also be relevant and have not been tested sufficiently in the past.

Translation to Clinical Setting

When asked by the organizers which findings may be ready as targets for interventions that can nudge people toward better habits, the speakers from the session were careful to point out that most of the presented work is still at an early stage and is aimed at better understanding the kinds of mechanisms that could be targeted. Translation into clinical work may still be well in the future.

[68] Baumeister, R.F., and Heatherton, T.F. (1996). Self-regulation failure: An overview. *Psychological Inquiry 7,* 1-15.
[69] Wagner, D.D., Altman, M., Boswell, R.G., Kelley, W.M., and Heatherton, T.F. (2013). Self-regulatory depletion enhances neural responses to rewards and impairs top-down control. *Psychological Science 24*(11), 2262-2271.

Lasting Change

The work on first-learned behaviors shows that the initial behavior never gets completely erased. Therefore, it can be difficult to determine at which point an intervention has led to a successful change of the individual. Long-term follow-up, which can be accomplished by asking people to sign up for voluntary registries, is likely a key to understanding these questions better.

Environmental Contexts

Participants noted the importance of considering how the environment changes people, which was not discussed at this workshop. For example, family and societal factors influence drug use. This requires the design of interventions that work on the level of the environment. The SOBC program has indeed made an effort to bring together scientists that study interventions at these different levels in the past. Collaborations across these levels will be of great importance for the continued success of the SOBC program.

Perspective Presentation

Can Neurobiological Variables Be Useful in Understanding and Changing Human Behavior?

Carlo DiClemente, PhD, University of Maryland, Baltimore County

Neurobiological variables will be useful for research on behavioral change but their exact role remains to be determined. To be successful in that challenge, researchers must obtain a detailed understanding of the change process and related psychological constructs. This includes differentiating between intentional and imposed change, which are very different phenomena; studying different patterns of change (initiation, modification, cessation); and better understanding specific change-generating and generic change-regulating mechanisms. Researchers also must assume a holistic perspective that avoids reductionism, monism, dualism, or neurosciencism, and engage in multidisciplinary exchange of ideas.

Behavior change is a complex, multidimensional process involving cognitive, affective, physiological, social, cultural, self-control, and behavioral processes. It is best thought of as a multi-event process and not a single event. Successful behavior change therefore represents completion of a series of complex tasks (e.g., decision-making) that build on each other and can be accomplished more or less well (qualitative as well as quantitative elements).

Dr. DiClemente noted that the goal usually is to achieve a moderated and self-regulated behavior pattern. If individuals go to excess temporarily, then life provides feedback that leads to adjustments. Some individuals do well staying in the middle between extremes. Others shift between excess and absence of behaviors. Process variables are likely different in initiation or cessation of behaviors. He recalled a research study in which he sent a questionnaire to individuals in maintenance. Several of these subjects indicated that they were not interested in participating because they no longer wanted to think about their addictions. Individuals are often aware of the delicate balance between absence and excess. However, in anorexia, often

we see the tendency to go to excess with the thinking that if a little exercise is good, then more will always be better. Researchers must decide where in this delicate self-regulatory balance to set the goal and how to measure it. Abstinence, for example, is a very different outcome compared to reduction of an addictive behavior.

Dr. DiClemente further emphasized that imposed change does not appear to reflect the same processes seen in voluntary change.[70] People change voluntarily only when

- They become interested and concerned about the need for change.
- They become convinced that the change is in their best interest or will benefit them more than cost them.
- They organize a plan of action that they are committed to implementing.
- They take the actions necessary to make the change and sustain the change.

Relapse does not always have to be triggered by cues, but can be a problem of contemplation and decision-making. When the above tasks have not been done well, individuals may give up when faced with the actual challenge. To achieve success, these tasks therefore have to be completed adequately.

Dr. DiClemente identified several future priorities for consideration:

- Use greater discipline when differentiating causation, consequence, correlation, and co-occurrence
- Consider equifinality—many roads can lead to the same place
- Address the reciprocal and complex interactions that exist between behaviors and interventions. The relationship between abstinence self-efficacy and temptation predicts time to relapse. Craving can be overcome when confidence is high.
- Address the underlying change regulating processes. Self-control is central, and the concept of self-regulation (executive cognitive functioning; affect regulation) appears to underlie essentially all behavior change.

Dr. DiClemente emphasized the importance of distinguishing more carefully between mechanisms, markers, moderators, and mediators. He also required that mechanisms of change explain a broad range of phenomena. Scientists still do not understand how brief interventions can cause greater changes than more intensive interventions, and how teachable moments can induce non-linear change. Short-term success and long-term success pose different challenges, and researchers need a better understanding of treatment failures and recycling.

Learning from the past is important for the future. Simple interventions such as cutting the corpus callosum have taught scientists a lot about the enormous adaptive capacity of the human brain, and watching people recover from serious strokes teaches us a lot about the potential for neuroplasticity even in the aging human brain.

[70] Stotts, A.L., DiClemente, C.C., Carbonari, J.P., and Mullen, P.D. (1996). Pregnancy smoking cessation: A case of mistaken identity. *Addictive Behaviors 21*, 459-471.

Conclusion

The participants thanked the SOBC program for its efforts to bring scientists from diverse disciplines together in this workshop. They unanimously expressed excitement about new research opportunities created by recent progress in integrating the fields of neuroplasticity and behavior. Each field clearly has the potential to add significant value to the other.

There was considerable skepticism that strategies to further modify external rewards to achieve behavior change will be successful. Instead, participants requested more sophisticated approaches to identify individual mediators of behavioral change and to explore the states during which subjects may be more susceptible to change. They cautioned against overly reductionist approaches and emphasized the need to consider internal factors (e.g., neurobiological variables and trait differences) as well as external factors (e.g., patient-physician relationship, treatment context) when designing interventions.

Participants identified several general issues and future challenges for the field:

- A systematic endeavor is needed to identify the most promising neurobiological markers, moderators, and mediators across all levels.
- The peer review process may contribute to an over-emphasis on discovery and an insufficient focus on a careful assessment of features of available markers, including their sensitivity and specificity as predictors.
- Imprecise language has led to the conflation of markers, moderators, and mediators.
- Human behavioral studies that cannot infer causality can be informed by animal model studies. Increased use of such models can help to identify the neurobiological measures that constitute the best candidates for mediators.

Sustained behavioral change at all levels will only be achievable with intervention designs that take a holistic approach and include multiple levels of analysis and consideration of the environment in which the intervention occurs. The behavioral change research field is, therefore, exceptionally broad and requires collaboration across a very wide range of disciplines for maximal effect. In the past, there have been few opportunities or incentives for behavior change researchers to reach out to other scientists who could inform their work. However, both the SOBC and Basic Behavioral and Social Science Opportunity Network (OppNet) programs at NIH are highly appreciated initiatives that have begun to bridge this gap. Information learned through presentations and discussions at these types of meetings will inform future SOBC priorities and efforts.

APPENDIX 1: Agenda

September 23 (Monday)

8:15 a.m.	**REGISTRATION CHECK-IN**	
8:30 a.m.	**CHARGE TO THE PARTICIPANTS**	Minda Lynch Jonathan W. King
8:45 a.m.	**WELCOME REMARKS** **NIH COMMON FUND SOBC PROGRAM**	Patricia Grady Richard Hodes Richard Suzman
9:00 a.m.	**PERSPECTIVE PRESENTATION** What I gained by incorporating neurobiological concepts and measures into ongoing research on behavior change: An idiographic account	Warren Bickel
9:30 a.m.	**PANEL 1 RESEARCH TALKS** Races, rewards, and behavior change How motivation shapes memory: When is a carrot not a carrot?	 David Zald R. Alison Adcock
10:10 a.m.	**BREAK**	
10:30 a.m.	**PERSPECTIVE PRESENTATION** The utility of brain biomarkers for predicting and understanding behavior: Concepts, cautions, and new directions	Tor D. Wager
10:50 a.m.	**GROUP DISCUSSION**	Lisbeth Nielsen
11:30 a.m.	**LUNCH**	
1:00 p.m.	**PANEL 2 RESEARCH TALKS** Neurobiological correlates of craving and addiction relapse: Treatment targets and moderators Neurobiological predictors in interventions for behavior change	 Rajita Sinha Diana Martinez

1:40 p.m.	**PERSPECTIVE PRESENTATION** Designs and methods for studying mediating and and moderating neurobiological variables in behavior change outcome studies	David P. MacKinnon
2:00 p.m.	**GROUP DISCUSSION**	Susan Czajkowski
2:40 p.m.	**BREAK**	
3:00 p.m.	**PANEL 3 RESEARCH TALKS** Training induced changes in inhibitory control network activity What do neurobiological variables and measures *buy us* or *add* to research to understand behavior change with cognitive remediation? Emotional and cognitive mechanisms in treatment of mood and anxiety disorders	Elliot Berkman Matcheri S. Keshavan Amit Etkin
4:00 p.m.	**PERSPECTIVE PRESENTATION** The critical role of neurobiological variables in understanding and changing human behavior	Gregory A. Miller
4:20 p.m.	**GROUP DISCUSSION**	Varda Shoham
5:00 p.m.	**CLOSING REMARKS**	Minda Lynch Warren Bickel
5:15 p.m.	**ADJOURN**	

September 24 (Tuesday)

8:45 a.m.	**INTRODUCTORY COMMENTS**	Minda Lynch Warren Bickel
9:00 a.m.	**PANEL 4 RESEARCH TALKS** Brief intervention improves self-control and neuroplasticity: Mechanism and application Persistent behavior change through automatic mechanisms Real time fMRI feedback and smoking cessation Biomarkers for self-regulation failure	Yi-Yuan Tang Russell Poldrack Mark S. George Kathleen T. Brady Todd F. Heatherton
10:20 a.m.	**GROUP DISCUSSION**	Minda Lynch

11:00 a.m.	**BREAK**	
11:20 a.m.	**PERSPECTIVE PRESENTATION** Can neurobiological variables be useful in understanding and changing human behavior?	Carlo DiClemente
11:40 a.m.	**SYNTHESIS OF PRESENTATIONS AND DISCUSSION**	Steven Grant Judith Rumsey
12:10 p.m.	**CLOSING REMARKS AND NEXT STEPS**	Minda Lynch Warren Bickel
12:30 p.m.	**ADJOURN**	

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